



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 23

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 23

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

This volume contains two articles which bring up to date older reviews in the Series. Progress in the chemistry of the 1,3-oxazines since they were covered by Eckstein and Urbański in Volume 2 (1963) is described by the same authors. Acheson and Elmore review reactions of acetylenecarboxylic esters with nitrogen heterocycles, which have been the subject of much concentrated research in the years since Acheson's article in Volume 1. The review on indolizines (Swinbourne, Hunt, and Klinkert) also concentrates on the advances of the last 15 years and up-dates reviews published elsewhere. Anastassiou and Kasmai provide a critical account of the " π -excessive heteroannulenes," and Fletcher and Siegrist deal authoritatively with the olefin-forming condensations of anils with methyl groups, the "Anil Synthesis."

A. R. KATRITZKY
A. J. BOULTON

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1,3-Oxazine Derivatives

Z. ECKSTEIN AND T. URBAŃSKI

*Chemical Faculty, Warsaw Institute of Technology (Politechnika),
Warsaw, Poland*

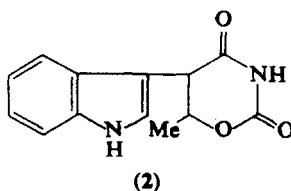
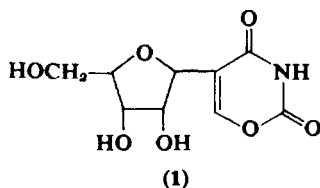
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I. Introduction

The continuous interest in the chemistry of 1,3-oxazines, manifested by numerous papers and patents, may be attributed to further evidence of the biological activity¹ of tetrahydro-1,3-oxazines, to the synthetic utility of 5,6-dihydro-4*H*-1,3-oxazines (due mainly to Meyers^{2,3} and Schmidt⁴), and to the discovery that some antibiotics contain the 1,3-oxazine ring, e.g., Oxazinomycin (**1**)⁵ (see also Section V,A,1).

It was also of interest that the antibiotic Indolmycin (from *Streptomyces albus*) on acid degradation furnished an indolyl derivative of 1,3-oxazine-2,4-dione (**2**).⁶ The continuation of the work of Kjaer *et al.*^{1,7} led to the finding that enzymatic hydrolysis of some naturally



occurring glucosinates produced isothiocyanates that readily undergo spontaneous or base-induced cyclization to tetrahydro-1,3-oxazine-2-thiones.

¹ Z. Eckstein and T. Urbański, *Ad. Heterocycl. Chem.* **2**, 311 (1963).

² A. I. Meyers, "Heterocyclics in Organic Synthesis." Wiley, New York, 1974.

³ E. W. Collington, *Chem. Ind. (London)*, 987 (1973).

⁴ R. R. Schmidt, *Synthesis*, 333 (1972).

⁵ T. Haneishi, T. Okazaki, T. Hata, C. Tamuta, M. Namura, A. Naito, I. Seki, and M. Arai, *J. Antibiot.* **24**, 797 (1971).

⁶ M. Schach v. Wittenau and H. Els, *J. Am. Chem. Soc.* **83**, 4678 (1961).

⁷ A. Kjaer and A. Schuster, *Acta Chem. Scand.* **24**, 1631 (1970).

The present review deals with the chemistry of 1,3-oxazine derivatives from 1962 until 1975. The literature up to 1962 was covered by our previous review.¹ Some papers published before 1962 but omitted therein are also quoted. We apologize for any work overlooked in the present review.

II. Methods of Preparation of 1,3-Oxazine Derivatives

Schmidt⁴ systematically classified methods of synthesis of some unsaturated 1,3-oxazines. We use the same system for all 1,3-oxazines.

A. TETRAHYDRO-1,3-OXAZINES

1. Methods of Cyclization

The main ring syntheses of tetrahydro-1,3-oxazine derivatives are summarized by diagrams **a** to **d** (Fig. 1). Two additional methods comprise the cyclization of six-membered chains, and the hydrogenation or

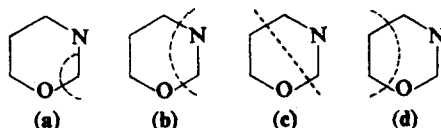
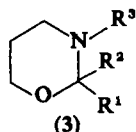


FIG. 1. Diagram of ring closure to form tetrahydro-1,3-oxazines.

other additions to unsaturated 1,3-oxazines.

a. Ring Closure a. The ring closure of 3-aminopropanol derivatives with aldehydes and ketones has become a conventional method of forming tetrahydro-1,3-oxazines of general formula 3.



Many papers and patents cover the formation of tetrahydro-1,3-oxazines from 3-aminopropanols and aldehydes or ketones.⁷⁻³⁴ Aliphatic, aromatic, or heterocyclic aldehydes introduced the corresponding

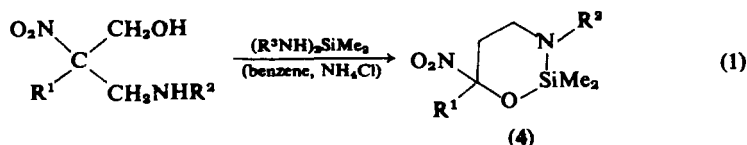
⁸ A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 1510 (1950).

⁹ J. S. Eden, U.S. Patent 2,911,294 [*CA* 54, 3842 (1960)].

¹⁰ W. J. Croxall, (Miles Labs. Inc.) French Patent 1,221,977 [*Chem. Zentr.*, 6209 (1962)].

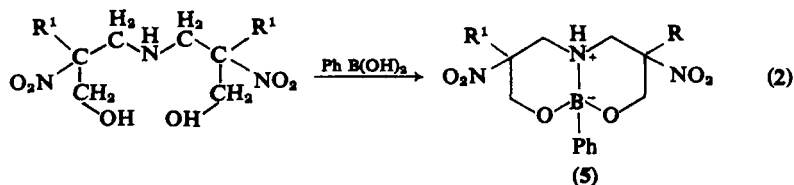
substituents in position 2. The reaction is usually carried out in an organic solvent in the presence of a catalytic quantity of a mineral acid, and water formed in the course of the reaction is removed by azeotropic distillation.

3-Aminopropanol derivatives also cyclized with reactive compounds containing a heteroatom to introduce the latter into position 2 of the ring. Thus, from 2-alkyl-3-amino-5-nitropropanol and bis(dialkylamino)-dimethylsilane, 5-nitrotetrahydro-2,1,3-silaoxazine (4)³⁵ was formed [Eq. (1)].

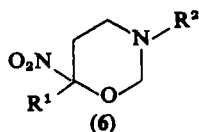


- ¹¹ Miles Labs., British Patent 889303 [CA 58, 1347 (1963)].
- ¹² A. S. Orahovats, *Monatsh. Chem.* **96**, 1446 (1965).
- ¹³ G. Fodor, J. Stefanowsky, and B. I. Kurtev, *Chem. Ber.* **98**, 705 (1965).
- ¹⁴ G. Fodor, J. Stefanowsky, and B. I. Kurtev, *Chem. Ber.* **100**, 3069 (1967).
- ¹⁵ Z. Horii, T. Inoi, S.-W. Kim, Y. Tamura, A. Suzuki, and H. Matsumoto, *Chem. Pharm. Bull.* **13**, 1151 (1965).
- ¹⁶ L. Turbanti, G. Cerbai, C. Bramanti, P. Bianchi, and N. Tellini, *Chem. Therap.* **2**, 354 (1967) [CA 69, 36048 (1968)].
- ¹⁷ J.-M. Lehn, P. Linscheid, and F. G. Ridell, *Bull. Soc. Chim. Fr.*, 1172 (1968).
- ¹⁸ F. G. Ridell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968).
- ¹⁹ Z. Horii and T. Inoi, Japanese Patent 18,465 [CA 69, 10449 (1968)].
- ²⁰ Eastman Kodak Co., French Patent 1,504,886 [CA 70, 57863 (1969)].
- ²¹ Krewel-Leuffen G.m.b.H., British Patent 1,059,666 [Chem. Zentr. **14**, 1404 (1969)].
- ²² Dynamit Nobel A. G., British Patent 1,152,560 [CA 71, 49951 (1969)].
- ²³ K. Thewalt and G. Reuckhoff (Dynamit Nobel A.G.), French Patent 1,560,931 [CA 72, 66929 (1970)].
- ²⁴ L. D. Taylor, P. McLaughlin, and M. Bach, *Org. Prep. Proc.* **2**, 33 (1970).
- ²⁵ H. Booth and R. U. Lemieux, *Can. J. Chem.* **49**, 777 (1971).
- ²⁶ R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc. B*, 1300 (1971).
- ²⁷ K. Eites, K. F. Hebenbrock, and M. Plempel, Ger. Offen. 2,035,797 [CA 76, 127001 (1972)].
- ²⁸ Farbenfabriken Bayer A.G., French Patent 2,082,275 [CA 77, 101629 (1972)].
- ²⁹ O. P. Boiko, Yu. F. Malina, and B. V. Unkovskii, *Khim. Tehnol. Tr. Yubileinoi Konf.* p. 161 (1972) [CA 81, 49532 (1974)].
- ³⁰ C. Fauran, C. Douzon, G. Huguet, G. Raynaud, and T. Bailly (Delalande S.A.), Ger. Offen. 2,221,408 [CA 78, 58435 (1973)].
- ³¹ C. Fauran, C. Douzon, G. Raynaud, and N. Dorme, French Demande 2,131,888 [CA 78, 124603 (1973)].
- ³² Yu. Yu. Samitov, B. V. Unkovskii, I. P. Boiko, O. I. Zhuk, and Yu. F. Malina, *Zh. Org. Khim.* **9**, 193 (1973).
- ³³ I. P. Boiko, Yu. E. Kazantsev, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 467 (1973).

In a similar way, dinitro-4-azaheptane-1,7-diols reacted with phenylboronic acid to yield isomeric cis- and trans-substituted diptychs with condensed 5-nitrotetrahydro-2,1,3-boraoxazine rings (5)^{36,37} [Eq. (2)].



b. *Ring Closure* b. This method has been particularly successful for preparation of 5-nitro-tetrahydro-1,3-oxazines (6), by reacting 2-nitropropane-1,3-diol with primary amines or ammonia and formaldehyde.^{1,37-58} This work has been summarized by Urbański.³⁷



³⁴ A. Rassat and P. Rey, *Tetrahedron* **30**, 3315 (1974); French Demande 2,219,146 [CA **82**, 156335 (1975)].

³⁵ M. Szretter-Szmid and T. Urbański, *Tetrahedron Lett.*, 2131 (1967).

³⁶ W. Daniewski and T. Urbański, *Tetrahedron, Suppl.* **8** (Part II), 663 (1966).

³⁷ T. Urbański, *Synthesis*, 613 (1974).

³⁸ T. Urbański, D. Gürne, R. Koliński, H. Piotrowska, A. Jończyk, B. Serafin, M. Szretter-Szmid, and M. Witanowski, *Tetrahedron* **20**, Suppl. 1, 195 (1964).

³⁹ D. Gürne, L. Stefaniak, T. Urbański, and M. Witanowski, *Tetrahedron* **20**, Suppl. 1, 211 (1964).

⁴⁰ Z. Eckstein, P. Gluziński, and T. Urbański, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.* **12**, 623 (1964).

⁴¹ T. Urbański, D. Gürne, B. Orłowska, and M. Mordarski, Polish Patent 5,1812 (1966); British Patent 1,098,759 (1968); Swedish Patent 314,374 (1969).

⁴² T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,007 (1967).

⁴³ T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,033 (1967).

⁴⁴ T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,035 (1967).

⁴⁵ T. Urbański, D. Gürne, M. Mordarski, and B. Orłowska, German (East) Patent 50,833 (1967) [*Chem. Zentr.* **48**, 1689 (1968)].

⁴⁶ I. Szczerek and T. Urbański, *IUPAC Congr., 21st, 1967 Abstr. Papers N-36; Carbohydr. Res.* **7**, 357 (1968).

⁴⁷ R. A. Koliński and T. Urbański, *J. Chem. Soc. C*, 1004 (1970).

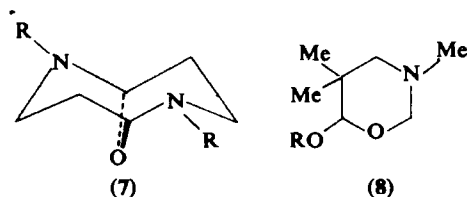
⁴⁸ A. Schmidt-Szałowska and T. Urbański, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **18**, 73 (1970).

⁴⁹ H. Piotrowska, T. Urbański, and K. Wejroch-Matacz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **19**, 359 (1971).

Using ammonia and formaldehyde as cyclizing agents, a fast reaction between them yields hexamethylenetetramine which gives an addition complex with 2-nitro-1,3-propanediol.⁵³ The components are here linked by hydrogen bonding.³⁷ The hexamethylenetetramine acts as a source of both formaldehyde and ammonia in a relatively slow reaction forming the tetrahydro-1,3-oxazine. There is a similarity with the mechanism described previously¹ for formation of 5-nitrotetrahydro-1,3-oxazines from 2-nitropropane-1,3-diol, formaldehyde, and primary amines through hexahydro-*s*-triazine intermediates.^{1,37}

A compound formerly reported⁵³ with an eight-membered oxazocine ring proved to contain a 2-nitrotetrahydro-1,3-oxazine ring, being a diastereoisomer of 5-ethyl-5-nitro-3-(2-nitrobutyl)tetrahydro-1,3-oxazine.^{1,37,47}

c. *Ring Closure c.* Mannich and Wieder⁵⁴ reacted isobutyraldehyde with formaldehyde and lower primary amines to give bicyclic compounds with two fused 1,3-oxazine rings (7). Johnson *et al.*^{55,56} modified the reaction conditions and obtained a high yield of 8 by reacting isobutyraldehyde with two molecules of formaldehyde and methylamine hydrochloride in an alcohol (ROH) in the presence of an acid.



d. *Ring Closure d.* This method, described previously,¹ consists in reacting olefins with formaldehyde and ammonium chloride. Recently, new compounds have been obtained.⁵⁷

⁵⁰ H. Piotrowska, T. Urbański, and K. Wejroch-Matacz, *Rocz. Chem.* **45**, 1267, 2107 (1971).

⁵¹ H. Piotrowska, T. Urbański, and W. Sienicki, *Rocz. Chem.* **47**, 193 (1973).

⁵² B. Kamiński, *Tetrahedron* **30**, 2777 (1974).

⁵³ E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochynski, A. T. Thomas, and T. Urbański, *J. Chem. Soc.*, 924 (1947).

⁵⁴ C. Mannich and H. Wieder, *Chem. Ber.* **65**, 385 (1932).

⁵⁵ P. Y. Johnson, R. B. Silver, and M. M. Davis, *J. Org. Chem.* **38**, 3753 (1973).

⁵⁶ P. Y. Johnson and R. B. Silver, *J. Heterocycl. Chem.* **10**, 1029 (1975).

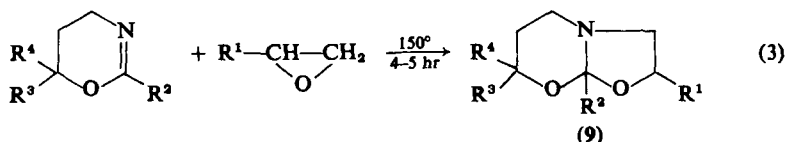
⁵⁷ R. Quelat and A-M. Touzin, *Ann. Chim.* **1**, 14, 107 (1966) [*Chem. Zentr.* **5**, 1026 (1968)].

⁵⁸ C. N. C. Drey and R. J. Ridge, *J. Chem. Soc., Chem. Commun.*, 948 (1975).

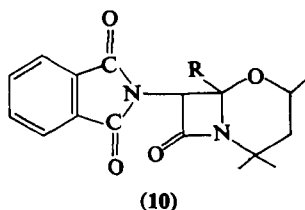
2. Hydrogenation or Other Addition to the Double Bond of Unsaturated 1,3-Oxazines

Numerous tetrahydro-1,3-oxazines have been prepared by Meyers *et al.*^{2,3} by reducing 5,6-dihydro-4*H*-1,3-oxazines with sodium borohydride. Catalytic hydrogenation of 5,6-dihydrooxazine-6-one failed to produce the tetrahydro derivative, as ring opening occurred.⁵⁸

Additions to the double bond of dihydro-1,3-oxazines can also produce bicyclic derivatives of tetrahydro-1,3-oxazines, such as **9**⁵⁹ [Eq. (3)]. Phthaloylglycyl chloride and dihydro-1,3-oxazines in the presence

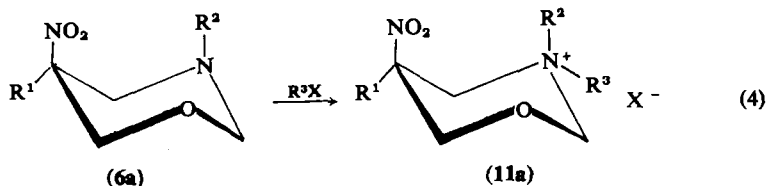


of triethylamine give the bicyclic system **10**.⁶⁰



3. Quaternary Salts: *N*-Oxides and Nitroxides

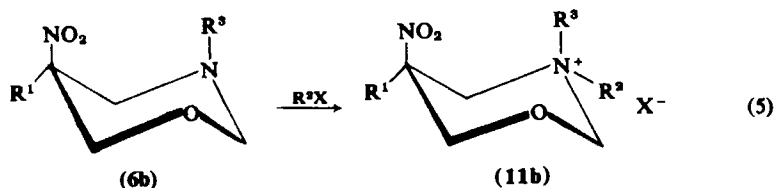
A number of diastereoisomeric pairs of quaternary salts of 5-nitro-tetrahydro-1,3-oxazine derivatives (**11a** and **11b**) were prepared by the action of *n*-alkyl bromides or iodides on 5-nitrotetrahydro-1,3-oxazines.⁶¹ The products contained at the 3-equatorial position the *n*-alkyl derived from the alkyl bromide (or iodide), **6a** and **6b** [Eqs. (4) and (5)].



⁵⁸ R. Feinauer and W. Seeliger, *Ann. Chem.* **698**, 174 (1966).

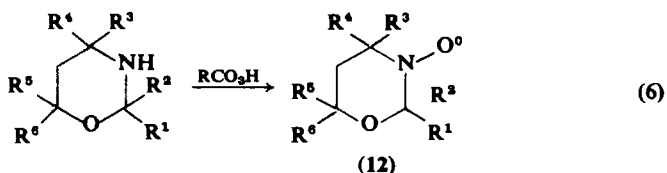
⁶⁰ J. C. Sheehan and M. Dadić, *J. Heterocycl. Chem.* **5**, 779 (1968).

⁶¹ D. Gürne, T. Urbański, M. Witanowski, B. Karniewska, and L. Stefaniak, *Tetrahedron* **20**, 1173 (1964).



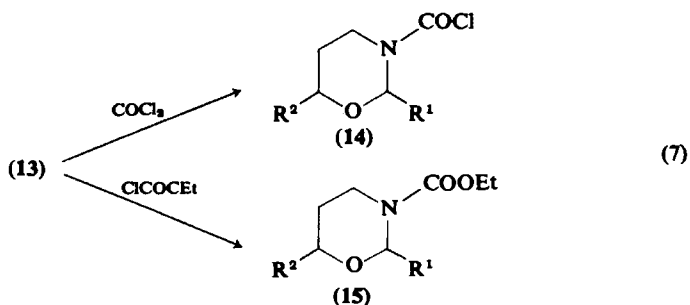
A few perchlorates of quaternary tetrahydro-1,3-oxazines were also described.⁸² Quaternary chlorides were prepared by direct cyclization of 3-dimethylaminopropanols with formaldehyde in hydrochloric acid.²³

A number of *N*-oxides have been obtained by oxidizing 5-nitrotetrahydro-1,3-oxazines (6) with peracetic acid.⁶³ Rassat and Rey⁸⁴ prepared nitroxides (12) from tetrahydro-1,3-oxazines with an NH group and *m*-chloroperbenzoic acid [Eq. (6)].



4. Other *N*-Substituted Derivatives

N-Nitroso compounds (13) have been obtained by the action of nitrous acid⁶⁴⁻⁶⁶ on tetrahydrooxazines (3; R³ = H). Compounds 13



⁶² B. C. Cossar and D. D. Reynolds, *J. Heterocycl. Chem.* **2**, 430 (1965).

⁶³ M. Mordarski, B. Chylińska, and T. Urbański, *Arch. Immunol. Ther. Exp.* **18**, 679 (1970).

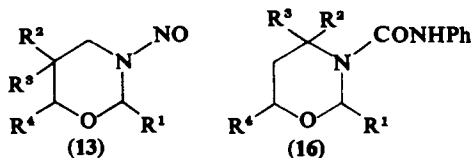
⁶⁴ K. Eiter, British Patent 1,276,623 [*CA* **77**, 88515 (1972)].

⁶⁵ Farbenfabriken Bayer A.G., French Patent 2,082,275 [*CA* **77**, 101629 (1972)].

⁶⁶ K. Eiter, U.S. Patent 3,709,882 [*CA* **78**, 72166 (1973)].

gave other N-substituted tetrahydro-1,3-oxazines,⁶⁷ e.g., **14** and **15**, using phosgene, chloroformic esters, oxalyl chloride, and similar halogen compounds [Eq. (7)].

Urea derivatives (**16**) were obtained from 3-unsubstituted tetrahydro-1,3-oxazines and aryl isocyanates.⁶⁸



Amides (**3**; $\text{R}^3 = \text{COR}^4$) were prepared by acylating **3** ($\text{R}^3 = \text{H}$) with acid chlorides⁶⁹ and also by cyclizing N-acylated 3-aminopropanols with aldehydes or ketones.⁷⁰

N-Unsubstituted tetrahydro-1,3-oxazines (**3**; $\text{R}^3 = \text{H}$) take part in Mannich-type reactions, e.g., 3-(2-nitrobutyl)-tetrahydro-1,3-oxazine^{1,37,47,53} and the corresponding bicyclic compound^{1,37} were thus obtained. A reaction with paraformaldehyde and acetophenone derivatives yields **3** ($\text{R}^1 = \text{H}$, alkyl, or Ph, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{COPh}$).^{71,72}

B. OXO AND THIONO DERIVATIVES OF TETRAHYDRO-1,3-OXAZINE

1. Methods of Cyclization

a. *Monooxo Compounds.* Cyclization to the oxo derivatives are similar to those for preparing tetrahydro-1,3-oxazines.

The most general method of preparing 2-carbonyl derivatives is to react 3-aminopropanols with difunctional derivatives of carbonic acid.¹ 2-Oxo derivatives of tetrahydro-1,3-oxazine being both δ -lactams and δ -lactones differ in their chemical properties from those of tetrahydro-1,3-oxazines.

⁶⁷ K.-F. Hebenbrock and K. Eiter, *Ann. Chem.* **765**, 78 (1972).

⁶⁸ G. R. Haynes and D. D. Phillips, U.S. Patent 3,558,615 [CA **75**, 63639 (1971)].

⁶⁹ L. Turbanti, G. Cerbai, G. Bramanti, P. Bianchini, and N. Tellini, *Chim. Ther.* **2**, 354 (1967) [CA **69**, 36048 (1968)].

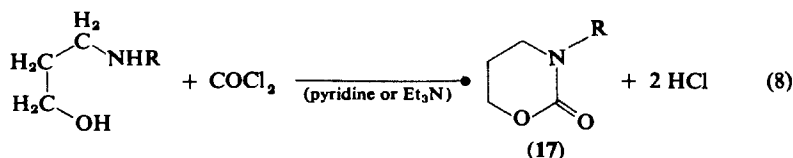
⁷⁰ K. Thewalt and G. Renckhoff, *Fette, Seifen, Anstrichm.* **70**, 648 (1968) [CA **71**, 30425 (1969)].

⁷¹ K. Kormendy, P. Sohár, and L. Torkos, *Acta Chim. Acad. Sci. Hung.* **40**, 333 (1964) [Chem. Zentr. **22**, 1089 (1968)].

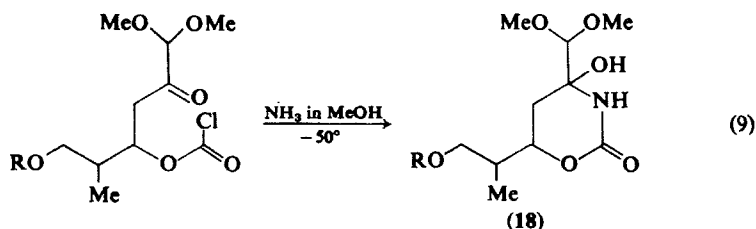
⁷² F. Hoffmann-La Roche A.G., Austrian Patent 251,598 [Chem. Zentr. **42**, 1442 (1969)].

N-Alkyl derivatives of 3-aminopropanol react readily with phosgene⁷³⁻⁷⁵ to yield **17** [Eq. (8)]; with $R^1 = H$ the reaction proceeds more readily.^{13,76} Ethyl chloroformate has also been used for cyclization.⁷⁷

2-Oxo analogs of **17** have been prepared similarly,^{78,79} and also from 3-halogenopropyl chloroformates and amines.⁸⁰ Meyers and Shaw⁸¹



obtained a more complex system (**18**) from a long-chain ketochloroformate and ammonia [Eq. (9)].



Simple oxo compounds (**17**) and their derivatives have also been prepared from 3-aminopropanols and carbonate esters: ethylene carbonate at 100°C⁸² or diethyl carbonate in the presence of alkali.^{83,84}

⁷³ W. Tuszko and T. Urbański, *Int. Symp. Nitro Compounds, 1963 Abstr.* p. 116; *Tetrahedron* **20**, Suppl. 1, 325 (1964).

⁷⁴ C. P. Fauran, C. Douzon, G. M. Raynaud, and M. Y. Sergant (Delalande S.A.), U.S. Patent 3,821,215 [*CA* **82**, 125412 (1975)].

⁷⁵ K. C. Murdoch, *J. Org. Chem.* **33**, 1367 (1968).

⁷⁶ A. Schmidt-Szałowska and T. Urbański, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **24**, 447 (1976).

⁷⁷ E. H. White, M. C. Chen, and L. A. Dolak, *J. Org. Chem.* **31**, 3038 (1966).

⁷⁸ K. Schmidt, Ger. Offen. 1,257,147 [*CA* **69**, 10447 (1968)].

⁷⁹ J. Maillard, M. Vincent, G. Remoud, Vo-Van Tri, and M. Rapin, *Chem. Ther.* **3**, 321 (1968) [*CA* **70**, 68280 (1969)].

⁸⁰ R. G. Haber (ABIC Chemical Labs., Ltd.), Canadian Patent 697,720 [*Chem. Zentr.* **43**, 2771 (1966)].

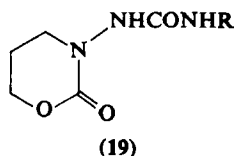
⁸¹ A. I. Meyers and Chia-Cheng Shaw, *Tetrahedron Lett.*, 717 (1974).

⁸² H. K. Hall and A. K. Schneider, *J. Am. Chem. Soc.* **80**, 6409 (1958).

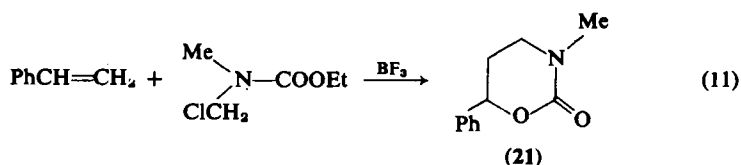
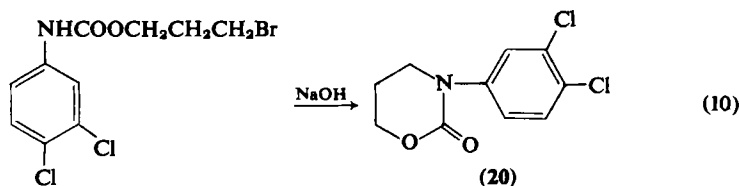
⁸³ Krewel-Leuffen G.m.b.H., British Patent 931,571 [*Chem. Zentr.* **29**, 2646 (1965)].

⁸⁴ Krewel-Leuffen G.m.b.H., Austrian Patent 231,454 (1964).

3-Hydroxy-*n*-propylhydrazine (3-hydrazylpropanol) was cyclized with ethyl carbonate to yield **17** ($R = NH_2$). The reaction was followed by treatment with isocyanate, $RNCO$, to form a urea derivative **19**.⁸⁵



Carbamate esters also produced 2-oxo compounds, e.g., the esters of 3-aminopropanol⁸⁶ and of 3-halogenopropanol.⁸⁷ A few compounds have thus been prepared from carbamates, e.g., **20**, with an aromatic substituent⁸⁸ [Eq. (10)] or a heterocyclic one.⁸⁹ Ethyl *N*-(3-hydroxypropyl) urethanes cyclize to 2-oxo compounds with sodium methoxide.⁷⁸ An interesting novel approach was to react an *N*-(chloromethyl)-carbamate with olefins to yield **21**⁹⁰ [Eq. (11)].



2-Oxo derivatives of **17** can be obtained via a Curtius degradation by the action of nitrous acid on γ -hydroxycarboxylic hydrazides, e.g., Eq. (12).^{91,92}

⁸⁵ E. K. W. Wat (du Pont de Nemours and Co.), U.S. Patent 3,859,301 [CA 82, 140151 (1975)].

⁸⁶ K. Schmidt, Ger. Offen. 1,257,147 [CA 69, 10447 (1968)].

⁸⁷ Norwich Pharmacal Co., British Patent 944,594 [Chem. Zentr. 36, 1783 (1966)].

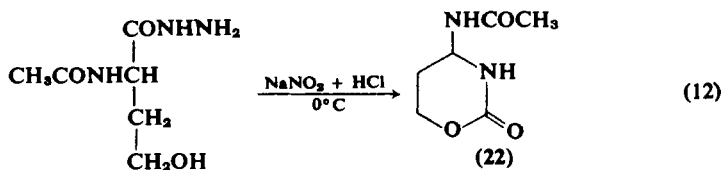
⁸⁸ P. J. Stoffel and A. J. Speziale, J. Org. Chem. 27, 3079 (1962).

⁸⁹ Norwich Pharmacal Co., Austrian Patent 233,000 [Chem. Zentr. 46, 1853 (1965)].

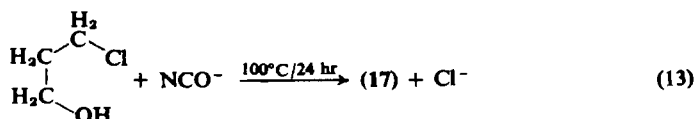
⁹⁰ R. Merten and J. Müller, Angew. Chem. 74, 866 (1962).

⁹¹ E. D. Nicolaides, J. Org. Chem. 32, 1251 (1967).

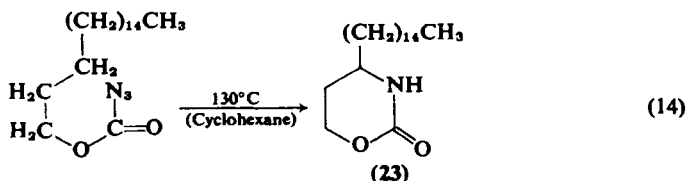
⁹² J. M. Sullivan and H. F. Efner, J. Org. Chem. 33, 2134 (1968).



3-Chloropropanol was also used to prepare **17** (R = H) by reaction with potassium cyanate in dimethylformamide [Eq. (13)].⁹³



Breslow⁹⁴ introduced an interesting method of forming 2-oxo compounds, which was based on his earlier work.⁹⁵ Thermolysis of *n*-octadecyl azidoformate gives some tetrahydro-1,3-oxazin-2-one (**23**) [Eq. (14)].



A new route to mono- and dioxo derivatives of 1,3-oxazine was given by Martin *et al.*^{96,97}: addition of 2 moles of ketene to the C=N of azomethines. (This reaction was described by Staudinger⁹⁸⁻¹⁰⁰ in 1906, but piperidinedione structures were assigned to these compounds.) When the Schiff's base PhCH=NEt reacted with 2 moles of dimethylketene a good yield of a derivative of 2-isopropylidenetetrahydro-1,3-

⁹³ B. L. Phillips and P. A. Argabright, *J. Heterocycl. Chem.* **3**, 84 (1966)].

⁹⁴ D. S. Breslow and G. A. Ward, *J. Org. Chem.* **38**, 4205 (1973).

⁹⁵ D. S. Breslow, T. J. Prossner, A. P. Marcantonio, and C. A. Genge, *J. Am. Chem. Soc.* **89**, 2384 (1967).

⁹⁶ J. C. Martin, V. A. Hoyle, and K. C. Brannock, *Tetrahedron Lett.*, 3589 (1965).

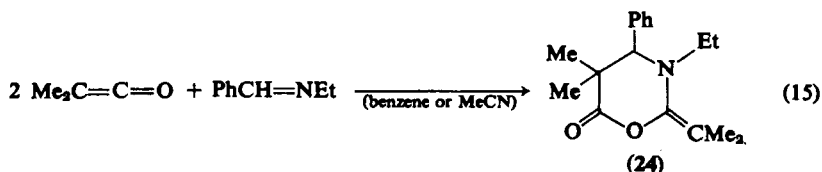
⁹⁷ J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Grott, and V. A. Hoyle, *J. Org. Chem.* **36**, 2211 (1971).

⁹⁸ H. Staudinger and H. W. Klever, *Chem. Ber.* **39**, 968 (1906); **40**, 1149 (1907).

⁹⁹ H. Staudinger, *Chem. Ber.* **39**, 3062 (1906); **40**, 1145 (1907).

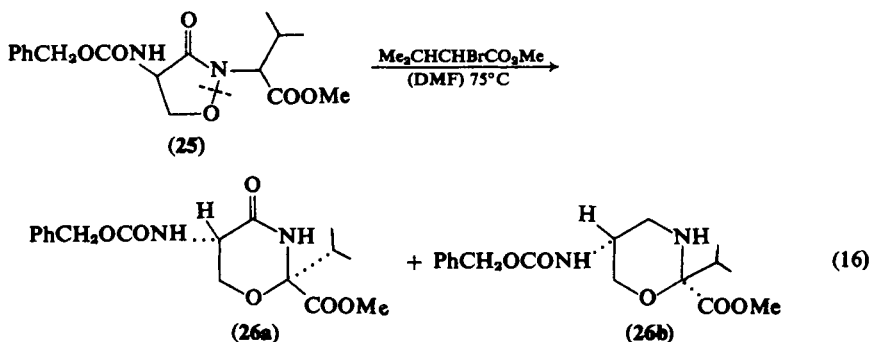
¹⁰⁰ H. Staudinger, H. W. Klever, and P. Kober, *Ann. Chem.* **374**, 1 (1910).

oxazin-6-one (**24**) resulted [Eq. (15)]. The formation of β -lactams competes,⁹⁶ and this is favored by solvents of low polarity.



A similar reaction with diphenylketene¹⁰¹ yields an analog of **24**. Diphenylketene also cycloadds to some heterocycles containing a C=N bond¹⁰² to form fused 1,3-oxazine rings. 1,3-Oxazin-4-one is also formed by condensation of a β -propiolactone with *p*-nitrobenzylideneaniline at 130° to 135°C in the presence of sodium acetate.¹⁰³

Enlargement of an isoxazolidine ring is also a method of forming 1,3-oxazin-4-ones.¹⁰⁴ A derivative (**25**) of the antibiotic cycloserine with methyl α -bromoisovalerate yielded two diastereoisomers, namely, **26a** and **b** [Eq. (16)], probably by ring cleavage of **25** as shown, followed by recyclization.



Farrissey and Nashu¹⁰⁵ reported that the reaction of an epoxide with phenyl isocyanate, which previously had been claimed to yield a tetrahydro-1,3-oxazin-2-one,^{1,106} produced, in fact, a 2-oxazolidone derivative.

¹⁰¹ R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem.* **80**, 802 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968).

¹⁰² M. J. Haddadin and A. Hassner, *J. Org. Chem.* **38**, 2650 (1973).

¹⁰³ F. I. Luknitskii and B. A. Vovsi, USSR Patent 195,457 [CA 68, 114582 (1968)].

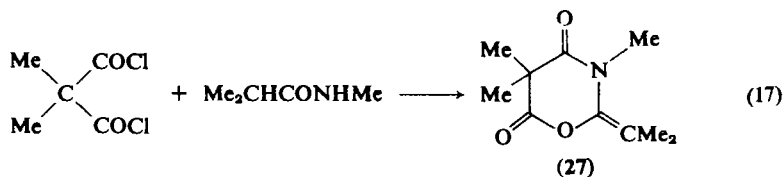
¹⁰⁴ R. B. Morin, J. R. Lake, and E. M. Gordon, *Tetrahedron Lett.*, 2979 (1974).

¹⁰⁵ W. J. Farrissey and A. M. Nashu, *J. Heterocycl. Chem.* **7**, 331 (1970).

¹⁰⁶ Y. Iwakura and Y. Taneda, *J. Org. Chem.* **24**, 1992 (1959).

b. *Dioxo Compounds.* β -Hydroxy acids¹ have continued to be a source of 2,4-dioxotetrahydro-1,3-oxazines.¹⁰⁷⁻¹⁰⁹ A modification consists in reacting β -hydroxypropiolactone with cyanic acid.¹¹⁰⁻¹¹² Hydrolysis of 2-imino-4-oxotetrahydro-1,3-oxazine also produced the 2,4-dioxo compound.¹¹³ As mentioned already, the product of the acid degradation of the antibiotic Indolmycin contains a 1,3-oxazine-2,4-dione unit.⁶

β -Amino acids and phosgene were used, as previously reported,¹ for the preparation of 2,6-dioxo derivatives.¹¹⁴ Reaction of dialkylmalonyl chloride with *N*-methylisobutyramide to yield **27** [Eq. (17)] is a general method of forming 4,6-dioxo derivatives of tetrahydro-1,3-oxazine, as reported by Martin *et al.*¹¹⁵



A diamide and malonyl chloride gave a compound with two dioxo-tetrahydro-1,3-oxazine rings.¹¹⁶ Diacylamines were also used to produce tetrahydro-1,3-oxazine-4,6-dione.¹¹⁷

c. *Trioxo Compounds.* The only trioxo derivative of tetrahydro-1,3-oxazine (**28**) was described recently.¹¹⁸ It was obtained by condensing a β -aminoacrylic ester with *N*-methyl bis(carbamyl chloride).

¹⁰⁷ E. Testa (Lepetit S.p.A.), Austrian Patent 212,323 [*Chem. Zentr.*, 12764 (1962)].

¹⁰⁸ E. Testa, Ger. Offen. 1,105,418 [*CA* 57, 3454 (1962)].

¹⁰⁹ Lepetit S.p.A., Indian Patent 69,607 [*Chem. Zentr.* 14, 1589 (1964)].

¹¹⁰ S. Ozaki and T. Kato, *J. Polym. Sci., Part C*, 695 (1966).

¹¹¹ Y. Miyake, S. Ozaki, and T. Kato, Japanese Patent 6808,278 [*CA* 69, 106719 (1968)].

¹¹² S. Ozaki and K. Kato, Japanese Patent 6,927,807 [*CA* 72, 43701 (1970)].

¹¹³ F. I. Luknitskii, B. A. Vovsi, and D. O. Taube, USSR Patent 222,394 [*CA* 70, 11705 (1969)].

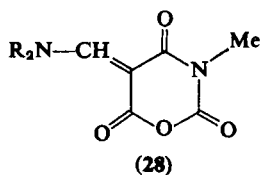
¹¹⁴ E. Testa, G. Cignarella, and G. Pifferi (Lepetit S.p.A.), Ger. Offen. 1,179,207 [*Chem. Zentr.* 30, 1834 (1965)].

¹¹⁵ J. C. Martin, K. C. Brannock, and R. H. Meen, *J. Org. Chem.* 31, 2966 (1966).

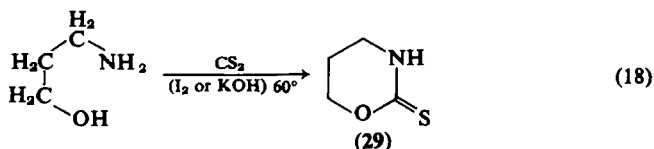
¹¹⁶ J. C. Martin and K. C. Brannock, U.S. Patent 3,373,159 [*CA* 69, 59254 (1968)].

¹¹⁷ H. W. Wittmann, A. Wohlkönig, H. Stark, and E. Ziegler, *Monatsh. Chem.* 101, 296 (1970).

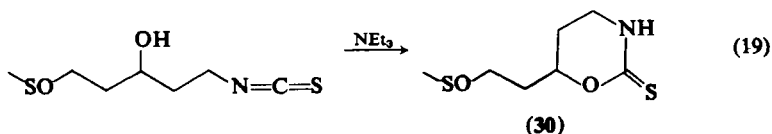
¹¹⁸ J. Grohe, Ger. Offen. 2,311,704 [*CA* 82, 4266 (1975)].



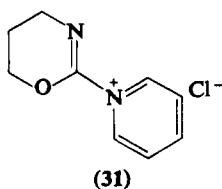
d. *Thiono Compounds*. A simple 2-thiono derivative (29) of tetrahydro-1,3-oxazine was obtained¹¹⁹ from carbon disulfide and 3-aminopropanol [Eq. (18)].



Kjaer and Schuster⁷ described the cyclization of the derivative of 3-hydroxypentyl isothiocyanate found in the seeds of *Erysimum hieracifolium* L. to a levorotatory tetrahydro-1,3-oxazine-2-thione (30) [Eq. (19)].



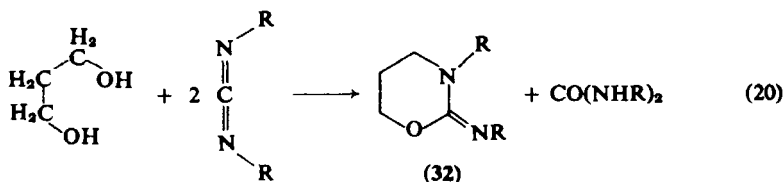
A novel method was recently reported of preparation of 2-thiones¹²⁰ by treating the pyridinium salt 31 with hydrogen sulfide.



¹¹⁹ M. Menard, A. W. Wringley, and F. L. Chub, *Can. J. Chem.* **39**, 273 (1961).

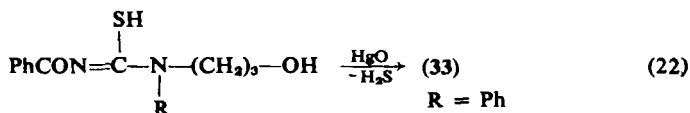
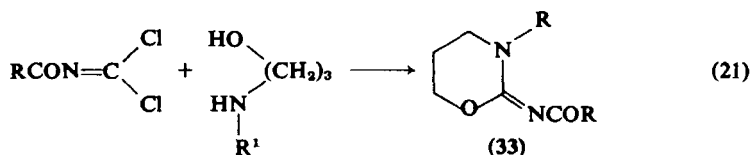
¹²⁰ A. Krantz and B. Hoppe, *Tetrahedron Lett.*, 695 (1975).

e. *Iminotetrahydro-1,3-oxazine Derivatives.* Carbodiimides produce 2-imino derivatives of tetrahydro-1,3-oxazine (32), for instance when condensed with propane-1,3-diol¹²¹ [Eq. (20)] or its cyclic ethers.¹²²

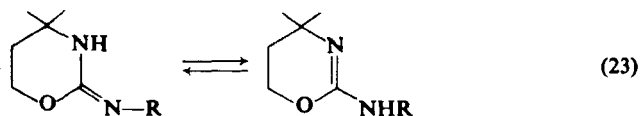


Carbodiimides with trimethyleneoxide and triethylamine¹²³ should produce compounds 32.

Other methods include condensing *N*-(dichloromethylene)carbamides with 3-aminoalcohols¹²⁴ [Eq. (21)] from thioureas to give 33¹²⁴ [Eq. (22)]; some imino compounds were prepared similarly.^{124,126}



According to Ignatova *et al.*,¹²⁵ 2-iminotetrahydro-1,3-oxazines are tautomeric with 2-amino-5,6-dihydro-4*H*-1,3-oxazines [Eq. (23)].



A novel method consists in reacting a β -propiolactone with *S*-alkyl isothiuronium salts¹²⁷ to give 2-imino-4-oxotetrahydro-1,3-oxazines.

¹²¹ E. Schmidt, E. Däbritz, K. Thulke, and E. Crassmann, *Ann. Chem.* **685**, 161 (1965).

¹²² E. Däbritz, *Angew. Chem.* **78**, 483 (1966).

¹²³ S. H. Metzger, U.S. Patent 3,479,351 [CA **72**, 21699 (1970)].

¹²⁴ J. Burkhardt and K. Hamann, *Chem. Ber.* **100**, 2569 (1967).

¹²⁵ L. A. Ignatova, A. E. Gekhman, P. L. Ovechkin, and V. B. Unkovskii, *Khim. Geterotsikl. Soedin.*, 354 (1974).

¹²⁶ Farbenfabrik Bayer A.G., French Patent 1,555,972 [CA **73**, 14861, 45496 (1970)].

¹²⁷ F. I. Luknitskii, B. A. Vovsi, and D. O. Taube, USSR Patent 222,393 [CA **70**, 11706 (1969)].

C. 5,6-DIHYDRO-4*H*-1,3-OXAZINES

As mentioned already, the interest in 5,6-dihydro-4*H*-1,3-oxazines is considerably increased by their use in the synthesis of aldehydes, ketones, and carboxylic acids.²⁻⁴ They are also useful protecting groups for reactions involving Grignard reagents.

1. *Methods of Cyclization*

Schmidt⁴ recently systematized existing syntheses of 5,6-dihydro-4*H*-1,3-oxazines into four general methods of ring closure (see diagrams a, b, c, and d of Fig. 2).

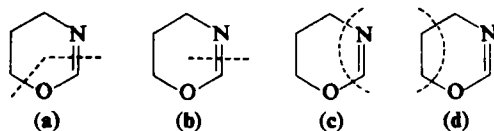
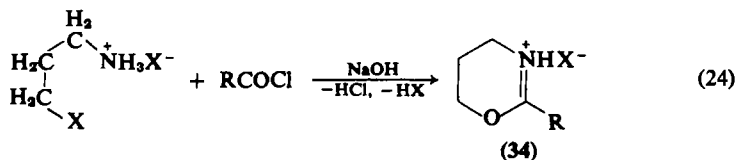
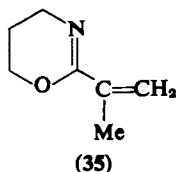


FIG. 2. Diagram of ring closure to form 5,6-dihydro-4*H*-1,3-oxazines.

a. The oldest method, condensing 3-halopropylamines with carboxylic acid chlorides¹, was extended¹²⁸ [Eq. (24)]. Further derivatives



(34) have since been obtained.^{129,130} Methacryloyl chloride gave 35,¹²⁹ which is suitable for further polymerization.

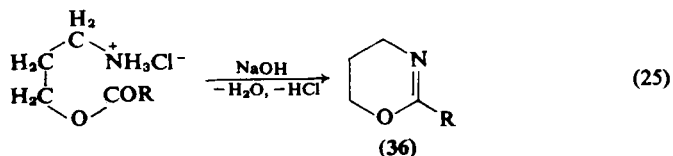


¹²⁸ S. Gabriel, *Ann. Chem.* **409**, 305 (1915).

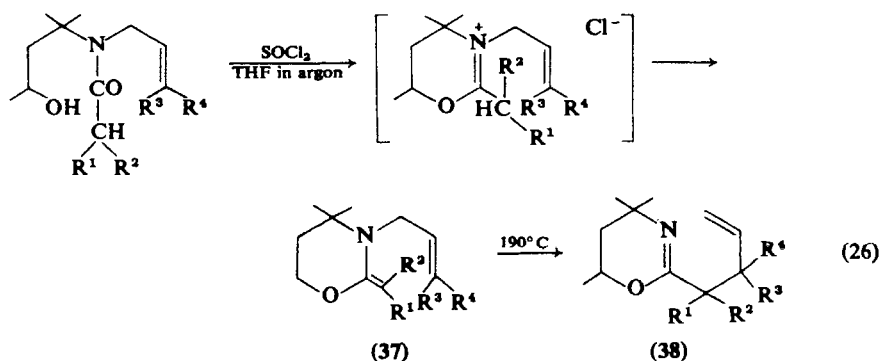
¹²⁹ L. S. Luskin and P. La Roche de Benneville (Rohm & Hass Co.), Ger. Offen. 1,067,437 [*Chem. Zentr.*, 19785 (1963)].

¹³⁰ C. Fauran, C. Douzon, G. Raynaud, and Y. Bailly (Delalande S.A.), French Demande 2,158,143 [*CA* **79**, 126509 (1973)].

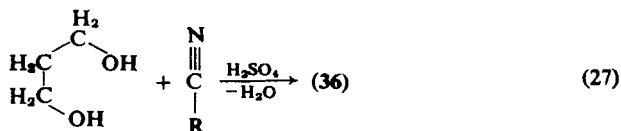
b. The method consists in treating an ester of 3-aminopropanol with alkali⁵ or 3-aminopropanol with a carboxylic acid derivative, as previously described¹ [Eq. (25)].



Cyclization of *N*-acylated 3-aminopropanol derivatives^{131,132} and of urea derivatives¹³³ belongs to the same category of reactions as do cyclization of isothioureas¹³⁴ and a novel cyclization followed by Claisen rearrangement of **37** into **38**¹³⁵ [Eq. (26)].



c. Nitriles cycloadd to propane-1,3-diol in the presence of a strong mineral acid^{1,136} [Eq. (27)]. Amides react similarly.¹ The mechanism of



¹³¹ M. H. Litt, R. B. Lund, J. Vitrone, J. L. Herz, and F. C. O'Donnel, U.S. Patent 3,681,333 [CA 77, 1,011,633 (1972)].

¹³² C. Fauran, C. Douzon, G. Raynaud, and B. Pourrias (Delalande S.A.), French Demande 2,215,223 [Ref. Zh. Khim. 170,103 P (1975)].

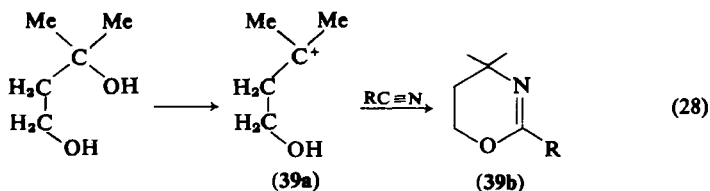
¹³³ A. Noriaki, J. Pharm. Soc. Jpn 82, 1547 (1962) [Chem. Zentr. 33, 0977 (1966)].

¹³⁴ L. A. Ignatova, P. L. Ovechkin, M. Z. Branzburg, A. E. Gekhman, and B. V. Unkovskii, Zh. Geterotsikl. Soedin., 1037 (1972).

¹³⁵ R. E. Ireland and A. K. Willard, J. Org. Chem. 39, 421 (1974).

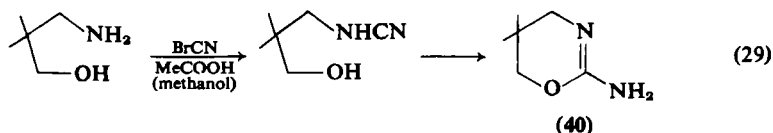
¹³⁶ Yu. M. Portiyagin and T. M. Pavel, Zh. Org. Khim. 11, 649 (1975).

the formation of **36** involves intermediate carbocation formation, e.g., **39a** [Eq. (28)].



3-Aminopropanol in the presence of salts of divalent metals^{137,138} similarly yields 5,6-dihydro-4*H*-1,3-oxazines.

An alternative route, to form the 2-amino compounds, by Meschino and Bond¹³⁹ used cyanogen bromide to cyclize aminopropanol [Eq. (29)] (see also Meschino and Poos¹⁴⁰).



Acrylonitrile took part in the cyclization to form **36** ($\text{R} = \text{CH}=\text{CH}_2$), which could be polymerized.¹⁴¹ Cyano- and chlorocynoacetylene were also used in the modified Ritter nitrile cycloaddition to produce 2-ethynyl- and 2-chloroethynyl-5,6-dihydro-4*H*-1,3-oxazines.¹⁴²

Unsaturated alcohols, e.g., $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, cyclize with R-CN in the presence of concentrated sulfuric acid.¹⁴³

Meyers *et al.*¹⁴⁴ gave an ingenious method of forming a 5,6-dihydro-4*H*-1,3-oxazine with the ultimate aim of producing azasteroids: nitriles react with cyclopentenyl-*t*-butanol (**41**) in the presence of sulfuric acid

¹³⁷ H. Witte and W. Seeliger, Ger. Offen. 2,127,776 [CA 78, 97627 (1973)].

¹³⁸ J. E. Kmiecik and H. Schulze, U.S. Patent 3,741,961 [Ref. Zh. Khim, 10N, 161P (1974)].

¹³⁹ J. A. Meschino and C. I. Bond, J. Org. Chem. 28, 3129 (1963).

¹⁴⁰ J. A. Meschino and G. J. Poos (McNeil Lab., Ind.), U.S. Patent 3,115,494 [Chem. Zentr. 32, 1686 (1966)].

¹⁴¹ M. A. Perry, J. B. Dickey, and A. G. Robinson (Eastman Kodak Co.), U.S. Patent 2,968,657 [Chem. Zentr. 46, 2541 (1966)].

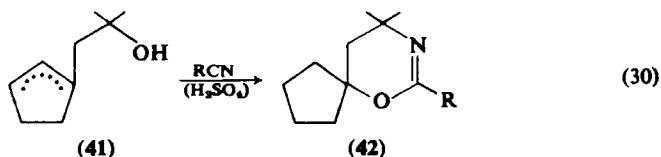
¹⁴² T. Sasaki, S. Eguchi, and S. Shoji, Bull. Chem. Soc. Jpn. 46, 540 (1973) [CA 78, 124525 (1973)].

¹⁴³ Laboratories Dausse, French Patent 1,241,140 [Chem. Zentr. 13, 1576 (1964)].

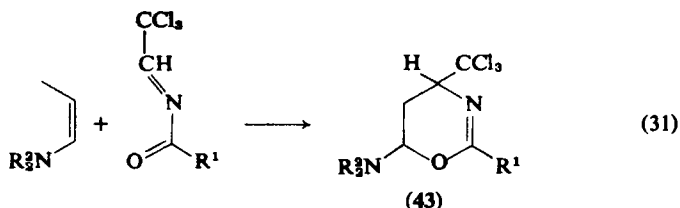
¹⁴⁴ A. I. Meyers, J. Schneller, and N. K. Ralhan, J. Org. Chem. 28, 2944 (1963).

to yield **42** [Eq. (30)]. Nitriles can also react with 3-aminopropanol to yield 5,6-dihydro-4*H*-1,3-oxazines with elimination of ammonia.¹⁴⁵

Isocyanates also cyclize with 3-chloropropylamine¹⁴⁶ and isothiocyanates with 3-aminopropanol¹³⁴ to yield derivatives of **36**.



d. The method involves Diels–Alder-type addition of *N*-acylimines with olefins. *N*-Acylimines are rather unstable compounds,^{4,144} but they possess electrophilic character and react with nucleophilic dienophiles, such as enamines,^{147–149} yielding **43** [Eq. (31)].



Subsequently it was shown that *N*-acylimines with their increased electrophilicity cycloadd to simple olefins,^{150–184} as predicted.⁴

¹⁴⁵ H. Witte and W. Seeliger, *Angew. Chem.* **84**, 343 (1972).

¹⁴⁶ H. J. Pander and H. Kiefer, Ger. Offen. 2,049,160 [*CA* **77**, 19655 (1972)].

¹⁴⁷ R. R. Schmidt and E. Schlipf, *Chem. Ber.* **103**, 3783 (1970).

¹⁴⁸ N. P. Gambaryan and Yu. V. Zeifman, *Izv. Akad. Nauk. SSSR* 2059 (1969).

¹⁴⁹ H. E. Zaugg, *Synthesis*, 49 (1970).

¹⁵⁰ R. R. Schmidt, *Chem. Ber.* **98**, 334 (1965).

¹⁵¹ R. R. Schmidt, *Angew. Chem.* **81**, 576 (1969); *Angew. Chem. Int. Ed. Engl.* **8**, 602 (1969).

¹⁵² R. R. Schmidt and R. Machat, *Angew. Chem.* **82**, 322 (1970); *Angew. Chem., Int. Ed. Engl.* **9**, 311 (1970).

¹⁵³ W. Seeliger and W. Diepers, *Ann. Chem.* **697**, 171 (1966).

¹⁵⁴ W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, *Angew. Chem.* **78**, 913 (1966); *Angew. Chem., Int. Ed. Engl.* **5**, 87 (1966).

¹⁵⁵ Chemische Werke Huels A.G., French Patent 1,478,076 [*CA* **68**, 78296 (1968)].

¹⁵⁶ K. Bott, *Tetrahedron Lett.*, 4185, 4301 (1970).

¹⁵⁷ R. R. Schmidt, *Chem. Ber.* **103**, 3242 (1970).

¹⁵⁸ Chemische Werke Huels A.G., French Patent 1,585,475 [*CA* **74**, 42365 (1971)].

¹⁵⁹ C. Giordano, G. Ribaldone, and G. Borsotti, *Synthesis*, 92 (1971).

¹⁶⁰ B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, and M. F. Tarasova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2324 (1972).

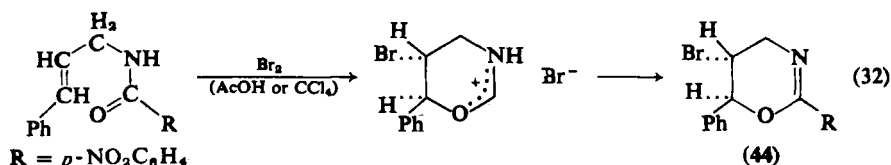
N-Hydroxymethyl amides are potential acylimines¹⁵²⁻¹⁵⁴ and react in a strongly acid medium (usually acetic and sulfuric acids) at ca. 10°C, probably as a carbonium-immonium ion:



A modification consists of reacting amides with aldehydes and olefins.¹⁵⁷⁻¹⁵⁸

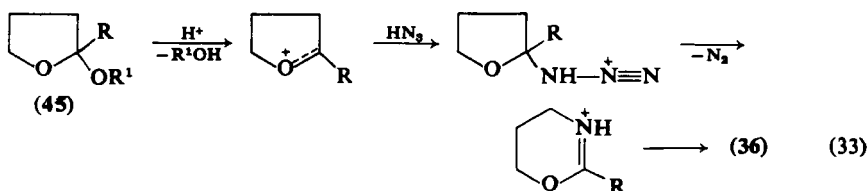
Another general method, mentioned in our earlier review,¹ of formation of 5,6-dihydro-4*H*-1,3-oxazines is the reaction of 3-azidopropanol and aromatic aldehydes.

Also cyclization of a six-membered chain has been reported. By brominating nonconjugated allylic amides, McManus *et al.*^{165,166} obtained 5,6-dihydro-1,3-oxazine derivative in addition to two other compounds (a five-membered ring and the brominated amide) [Eq. (32)].



2. Ring Enlargement

Recently the tetrahydrofuran ring of a hemiacetal (45) was enlarged¹⁶⁷ by inserting nitrogen from hydrazoic acid to obtain 36 [Eq. (33)]. This method was used for the formation of a 5,6-dihydro-4*H*-1,3-oxazine steroid.



¹⁶¹ A. D. Sinitsa, B. S. Drach, and A. A. Kisilenko, *Zh. Org. Khim.* **9**, 685 (1973).

¹⁶² M. Pánková and M. Tichý, *Coll. Czech. Chem. Commun.* **39**, 1447 (1973).

¹⁶³ Yu. A. Arbuzov, E. I. Klimova, N. D. Antonova, and Yu. V. Tomilov, *Zh. Org. Khim.* **10**, 1164 (1974).

¹⁶⁴ R. R. Schmidt and A. R. Hoffman, *Chem. Ber.* **107**, 78 (1974).

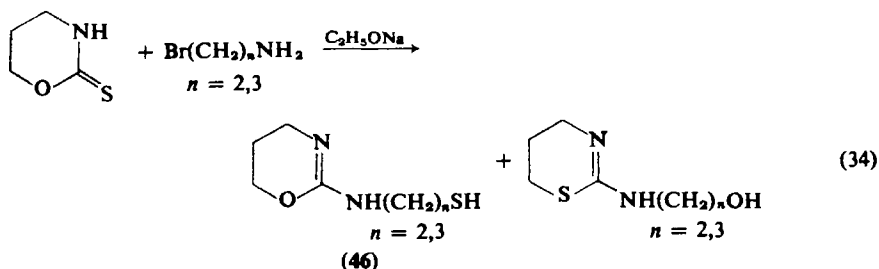
¹⁶⁵ S. P. McManus and R. A. Hames, *Tetrahedron Lett.*, 4549 (1973).

¹⁶⁶ S. P. McManus and D. W. Ware, *Tetrahedron Lett.*, 4271 (1974).

¹⁶⁷ C. Monneret, P. Choay, and O. Khuong-Huu, *Tetrahedron* **31**, 575 (1975).

3. Reactions of 2-Thione Derivatives

Tetrahydro-1,3-oxazine-2-thione reacts with rearrangement to yield **46** and a thiazine¹⁶⁸ [Eq. (34)].

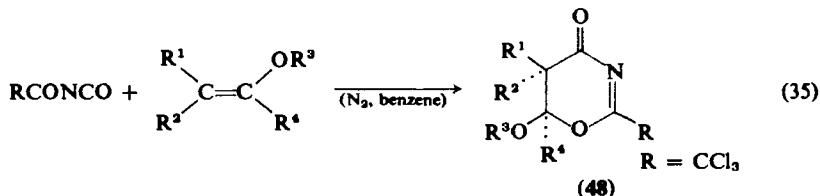


Thione derivatives can be *S*-methylated. Thus the tetrahydro-1,3-oxazine-2-thione with methyl iodide yielded 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (**47**).



D. OXO DERIVATIVES OF 5,6-DIHYDRO-4*H*-1,3-OXAZINES

Of the new methods of preparation of oxo derivatives of the 5,6-dihydro-4*H*-1,3-oxazines, the most important is that developed by Martin and co-workers:¹⁶⁹ the reaction of acylisocyanates with enol ethers at room temperature under nitrogen yields **48** [Eq. (35)] (see also Arbuzov *et al.*^{170,171}) together with an isomeric azetidinone. The



¹⁶⁸ R. C. Clapp and L. Long, *J. Heterocycl. Chem.* **7**, 1357 (1970).

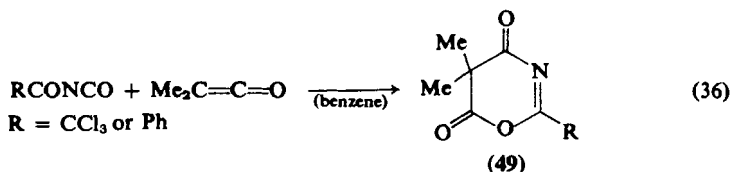
¹⁶⁹ J. L. Chitwood, P. G. Gott, and J. C. Martin, *J. Org. Chem.* **36**, 2228 (1971).

¹⁷⁰ B. A. Arbuzov, N. N. Zubova, and F. B. Balabanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2086 (1972).

¹⁷¹ B. A. Arbuzov, N. N. Zubova, and I. I. Adrianova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1566 (1974).

product ($R = \text{CCl}_3$) is extremely hygroscopic and subject to ring opening under acid conditions.

By reacting an acylisocyanate with dimethylketene, 4,6-dioxo derivatives of 1,3-oxazine (49) were obtained¹⁷² [Eq. (36)]. The reaction is exothermic and the temperature was kept below 40°C.



An earlier work of Barker¹⁷³ described the formation of 5,6-dihydro-4-methyl-6-oxo-2,4-diphenyl-1,3-oxazine through dehydration of β -benzamido- β -phenylbutyric acid with acetic anhydride.

Steglich *et al.*¹⁷⁴ obtained 5,6-dihydro-4*H*-1,3-oxazin-6-one by pyrolysis (270°C) of ethyl β -acylaminocrotonate. Ethanol is evolved and a ketene is formed as an intermediate.

E. 3,4-DIHYDRO-2*H*-1,3-OXAZINES

By a method similar to one previously described,¹ a new 2-spiro derivative of 3,4-dihydro-2*H*-1,3-oxazine was obtained¹⁷⁵ by the cyclization of phenylcyanopyruvic ester with cyclohexanone. Also a 3,4-dihydro derivative was found as a by-product in the formation of a 5,6-dihydro derivative.³³

F. OXO DERIVATIVES OF 3,4-DIHYDRO-2*H*-1,3-OXAZINES

A relatively large number of papers has described the preparation of oxo derivatives of 3,4-dihydro-2*H*-1,3-oxazine. The previously reported¹ use of diketene as a cyclizing agent has found wider application. Gunar *et al.*¹⁷⁶ described the reaction of diketene with ammonium thiocyanate. It passes through an intermediate acetoacetyl isothiocyanate to a 2-thiono derivative, which, on oxidation, yields 50 [Eq. (37)].

¹⁷² J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris, and R. H. Meen, *J. Org. Chem.* **36**, 2205 (1971).

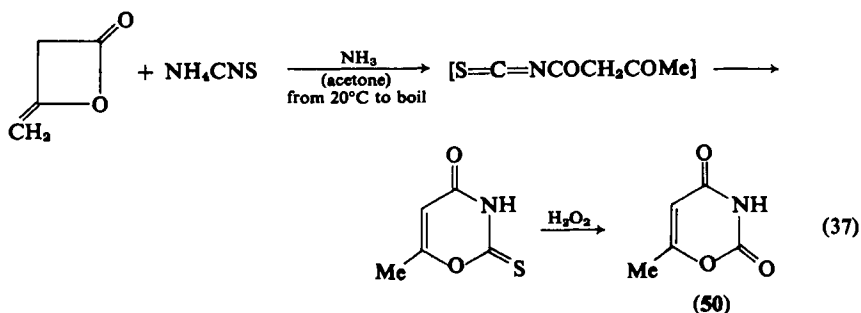
¹⁷³ C. C. Barker, *J. Chem. Soc.*, 317 (1954).

¹⁷⁴ W. Steglich, E. Buschmann, and O. Hollitzer, *Angew. Chem.* **86**, 596 (1974).

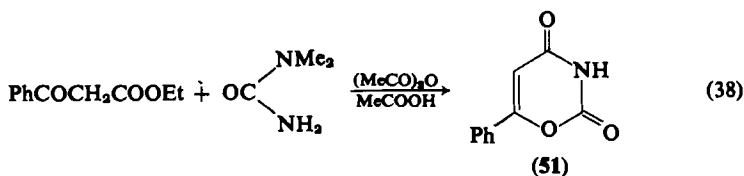
¹⁷⁵ P. Cordier, L. Jung, and R. Hug, *Ger. Offen.* 2,241,271 [*CA* **78**, 159,632 (1973)].

¹⁷⁶ V. I. Gunar, L. F. Ovechkina, and S. I. Zavyalov, *Izv. Akad. Nauk SSSR*, 1076 (1965).

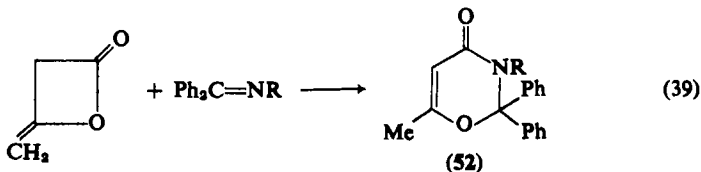
They also described the reaction of diketene with *N,N*-dimethylurea in acetic acid, yielding **50** (see also Ahmed *et al.*¹⁷⁷). Gunar *et al.*¹⁷⁸ used diketene in the reaction with cyanic acid (see also Ozaki¹⁷⁹), thiocyanic acid, ethyl urethane, and *N,N'*-disubstituted ureas in acetic acid medium to obtain **50**. When a 2-thiono derivative was obtained from thiocyanic acid, as in Eq. (37), they desulfurized it with mercuric acetate.



The reaction of diketene with aryl isocyanates in an acid medium furnished derivatives of **50**.^{180,181} It was also found that acetoacetic and benzoylacetic esters react with unsymmetrical dimethylurea to yield **50** and **51**, respectively [Eq. (38)].



Diketene reacts with Schiff's bases¹⁸² to yield a monooxo product (**52**) [Eq. (39)]. Acetoacetamide reacts similarly.¹⁸²



¹⁷⁷ S. Ahmed, R. Lofthouse, and G. Shaw, *J. Chem. Soc. Chem. Commun.*, 959 (1974).

¹⁷⁸ V. I. Gunar, I. A. Mikhailopulo, L. F. Ovechkina, and S. I. Zavyalov, *Kh. Geterotsikl. Soedin.*, 48 (1967).

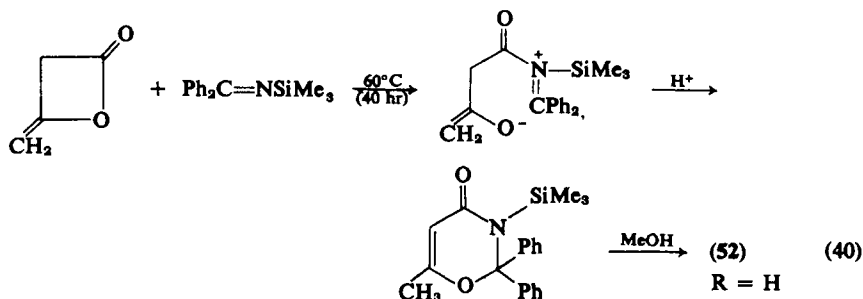
¹⁷⁹ S. Ozaki, Japanese Patent 69 12735 [*CA* 71, 91490 (1969)].

¹⁸⁰ S. Ozaki, Japanese Patent 70 21663 [*CA* 74, 53811 (1971)].

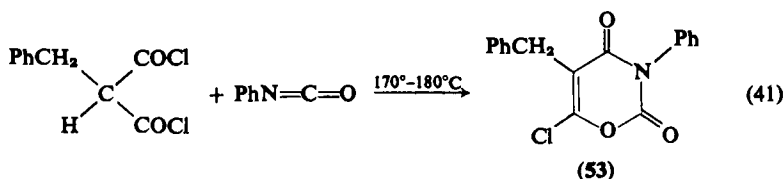
¹⁸¹ S. Ozaki, Japanese Patent 70 37018 [*CA* 74, 64251 (1971)].

¹⁸² T. Kato and T. Sakamoto, *Yakugaku Zasshi* 87, 1322 (1967) [*CA* 68, 114524 (1968)].

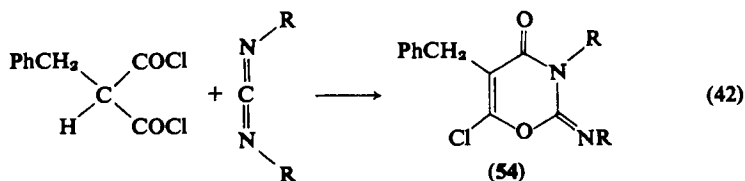
A novel approach to the reaction of diketene with compounds possessing a C=N bond was given by Suzuki *et al.*¹⁸³ They treated diketene with *N*-trimethylsilyl(diphenylmethylene)amine. "Demetallation" with methanol eventually yielded **52** [Eq. (40)].



Monosubstituted malonyl chlorides can also be used to obtain 3,4-dihydro-1,3-oxazine-2,4-diones. Ziegler *et al.*¹⁸⁴ reported the formation of **53** by heating benzylmalonyl chloride with phenyl isocyanate [Eq. (41)]. By carrying out the reaction in the presence of stannic chloride, the temperature can be considerably lowered.¹⁸⁵ Mono-



substituted malonyl chlorides react with carbodiimides to form imino derivatives (**54**)¹⁸⁶ [Eq. (42)].



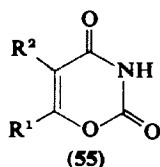
¹⁸³ H. Suzuki, I. Matsuda, K. Itoh, and Y. Ishii, *Bull. Chem. Soc. Jpn.* **47**, 2736 (1974).

¹⁸⁴ E. Ziegler, G. Kleineberg, and H. Meindl, *Monatsh. Chem.* **94**, 544 (1963); **97**, 10 (1966).

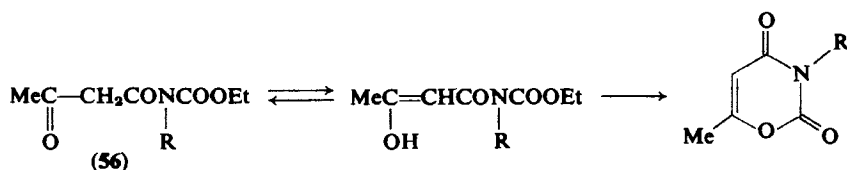
¹⁸⁵ H. Disseinkoetter, Ger. Offen. 1,940,368 [CA 74, 88003 (1971)].

¹⁸⁶ G. Kleineberg and E. Ziegler, *Monatsh. Chem.* **94**, 502 (1963).

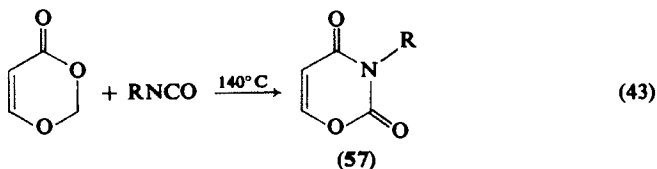
Aromatic ketones ($R^1COCH_2R^2$) can undergo electrophilic addition of chlorosulfonyl isocyanate ($ClSO_2NCO$) yielding eventually **55**.¹⁸⁷



N-Acetoacetyl urethanes (**56**) can be cyclized by concentrated sulfuric acid to yield 1,3-oxazine-2,4-dione derivatives.¹⁸⁸



A novel approach to the preparation of 3,4-dihydro derivatives was described recently.¹⁸⁹ It consists in heating 1,3-dioxin-4-one with isocyanates [Eq. (43)].



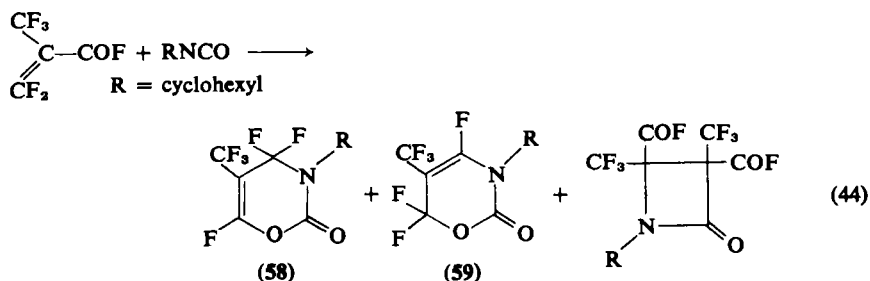
A fluorinated 2-oxo derivative of 3,4-dihydro-2*H*-1,3-oxazine (**58**) was obtained, along with a 2,3-dihydro derivative (**59**) and an azetidinone, from perfluoromethacryloyl fluoride and cyclohexyl isocyanate¹⁹⁰ [Eq. (44)].

¹⁸⁷ A. Hassner and J. R. Rasmussen, *J. Am. Chem. Soc.* **97**, 1451 (1975).

¹⁸⁸ R. N. Warrenner and F. N. Cain, *Tetrahedron Lett.*, 3231 (1966).

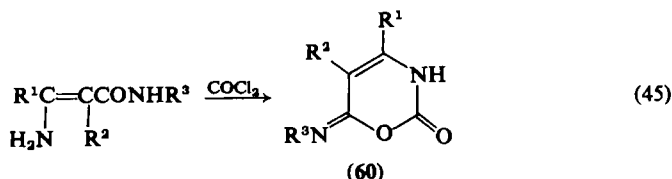
¹⁸⁹ G. Jaeger, J. Wenzelburger, and R. Wegler, *Ger. Offen.* 2,005,118 [*CA* **75**, 151812 (1971)].

¹⁹⁰ D. C. England and G. C. Krespan, *J. Fluorine Chem.* **3**, 91 (1973).



G. 2,3-DIHYDRO-6H-1,3-OXAZINES

Cyclization of a β -aminocrotonamide with phosgene led to the formation of a 2-oxo-6-imino derivative (60) of 2,3-dihydro-1,3-oxazine¹⁹¹ [Eq. (45)]. A fluorinated 2-oxo derivative of 2,3-dihydro-



2H-1,3-oxazine was obtained along with the 3,4-dihydro derivative as previously described¹⁹⁰ [Eq. (44)]. When methyl isocyanate (R = Me) was used for cyclization, only the 2,3-dihydro derivative resulted, along with the azetidinone [Eq. (44)]. Halogenated 2,6-dioxo derivatives were obtained by reacting trimethylsilylazide with halogenated maleic anhydride.¹⁹²

H. 4H-1,3-OXAZINES

4H-1,3-Oxazines were at the time of the previous review the only known 1,3-oxazine derivatives with two cyclic double bonds, but recently 2H-1,3- and 6H-1,3-oxazines have been described and will be referred to in separate paragraphs. A new group of 1,3-oxazine derivatives is the azapyrylium salts with three double bonds, and they too will be described in a separate section of the present review.

¹⁹¹ H. L. Kloppe and H. M. Loux, U.S. Patent 3,352,662 [CA 68, 114,610 (1968)].

¹⁹² J. D. Warren, J. H. MacMillan, and S. S. Washburne, J. Org. Chem. 40, 743 (1975).

1. Cyclization

Schmidt⁴ classified the synthetic routes to 1,3-oxazines with two double bonds as methods **a**, **b**, and **c** of Fig. 3. Prior to Schmidt, only

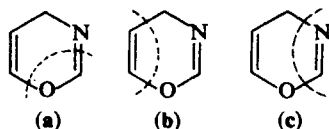
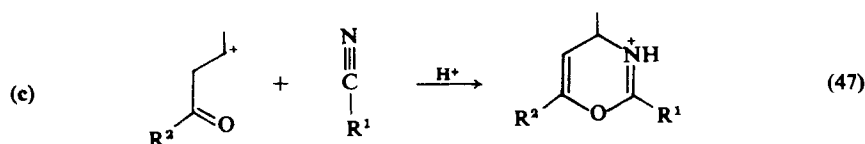
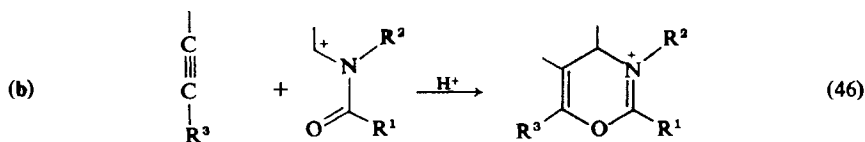


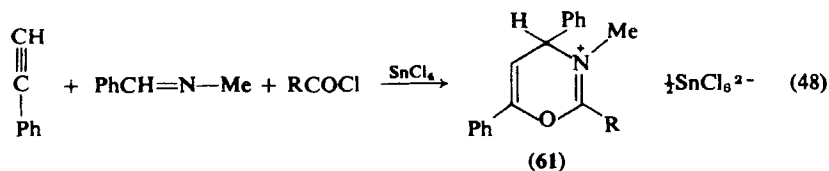
FIG. 3. Diagram of ring closure to form 4H-1,3-oxazines.

method **a** had been described in the literature.¹ Methods **b** and **c** both consist of the addition of 1,4-polar systems to acetylenic compounds and nitriles, according to Eqs. (46) and (47),⁴ respectively, yielding 4H-1,3-oxazinium salts.



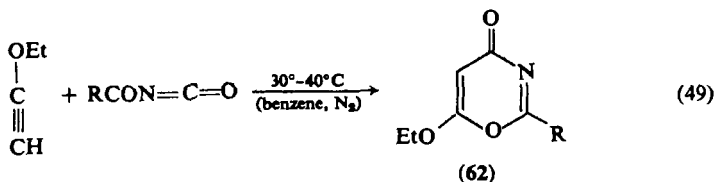
a. The best known method of forming 4H-1,3-oxazines is acylation of β -aminoketones followed by cyclization with phosphorus pentachloride,¹ phosphoric or oxalic acid.⁴

b. In the original method acetylenic compounds were used to react with amides,⁴ but in a modification¹⁹³ the amide was replaced by a Schiff's base and an acyl chloride in the presence of SnCl_4 [Eq. (48)], resulting in a 92% yield of the stannichloride (61).

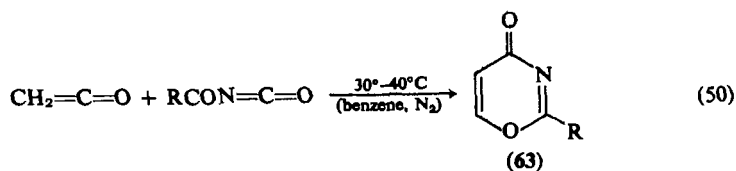


¹⁹³ R. R. Schmidt, *Angew. Chem.* **77**, 218 (1965); *Angew. Chem., Int. Ed. Engl.* **4**, 241 (1965).

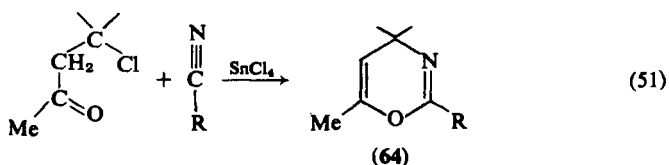
Oxo derivatives of 4*H*-1,3-oxazine can readily be obtained from acetylenic compounds and acyl isocyanates, e.g., to obtain **62**¹⁸⁹ in 85% yield. This is a [2 + 4] cycloaddition [Eq. (49)]. A number of 4*H*-1,3-oxazin-4-ones have been prepared by this method.^{189,194-197}



Acyl isocyanates can also react with ketene to give derivatives of 4*H*-1,3-oxazine (**63**)¹⁷² [Eq. (50)].



c. The method consists in reacting nitriles with β -chloroketones^{198,199} [Eq. (51)]. Nitriles can also react with mono-substituted malonyl



chlorides to yield 6-chloro-4-oxo derivatives of **64**.¹⁸⁴ Similar derivatives of 4*H*-1,3-oxazine can also be obtained from mono-substituted malonic

¹⁸⁴ R. R. Schmidt, *Chem. Ber.* **98**, 3892 (1965).

¹⁸⁵ H. J. Gais and K. Hafner, *Tetrahedron Lett.*, 5101 (1970).

¹⁸⁶ B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, and A. V. Fuzhenkova, *Dokl. Vses. Konf. Khim. Atsetilena* **1**, 500 (1972) [*Ref. Zh. Khim.* **3** Zh 355 (1973)].

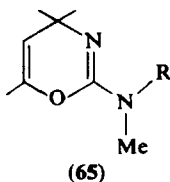
¹⁸⁷ B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, A. V. Fuzhenkova, and V. D. Pankratova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1580 (1973).

¹⁸⁸ M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, and H. Leipprand, *Chem. Ber.* **97**, 2234, 2244 (1964).

¹⁸⁹ M. Lora-Tamayo, D. Gracian, and V. Gomez-Parra, *Tetrahedron, Suppl.* **8**, Part I, 305 (1967).

acids and aromatic amides in the presence of phosphorus chlorides, thionyl chloride, or acetic anhydride.²⁰⁰

Ignatova *et al.*²⁰¹ described an interesting cyclization that differs from methods **a**, **b**, and **c**. The addition of methyl iodide to ketothiourea derivatives yields iodides of *S*-methylisothiureas that cyclize to 4*H*-1,3-oxazines of general structure **65**.

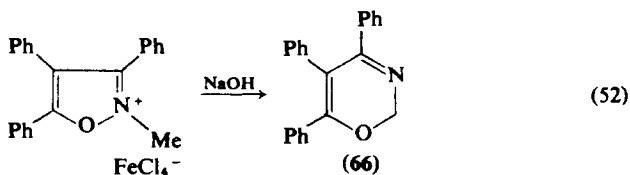


2. Addition with Proton Elimination

4*H*-1,3-Oxazine derivatives can be formed from 1,3-oxazinium salts substituted in positions 4, 5, and 6 by aromatic residues by addition of active CH compounds in position 6 of the oxazinium salt.⁴ The product can be subjected to further transformations [as described in Section III,F,2,c; Eq. (82)].

I. 2*H*-1,3-OXAZINES

The 2*H*-1,3-oxazine ring was first described by King and Durst²⁰² who revised earlier work of Kohler and Blatt²⁰³ and established that the "anhydro compounds" formed by the action of alkalis on isoxazolium salts are 2*H*-1,3-oxazines (**66**) [Eq. (52)]. The same ring system is obtained from an α -cyano- α -bromo ester with triisopropyl phosphite through an



²⁰⁰ E. Ziegler and H. Meindl, *Monatsh.* **95**, 1318 (1964).

²⁰¹ L. A. Ignatova, A. E. Gekhman, M. A. Spektor, P. L. Ovechin, and B. V. Unkovskii, *Zh. Geterotsikl. Soedin.*, 764 (1974).

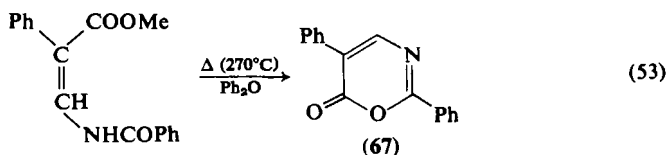
²⁰² J. P. King and T. Durst, *Can. J. Chem.* **40**, 882 (1962).

²⁰³ E. P. Kohler and A. H. Blatt, *J. Am. Chem. Soc.* **50**, 1217 (1928).

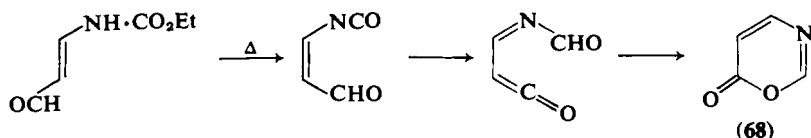
intermediate *N*-phosphorylated ketenimine, which readily cyclizes to the 1,3-oxazine.²⁰⁴

J. 6*H*-1,3-OXAZINES

The first representative of this group, a β -acylamino- α,β -unsaturated ester, yielded **67** through pyrolysis in diphenyl ether²⁰⁵⁻²⁰⁷ [Eq. (53)]. A modification of this method used a Schiff's base instead of the *N*-acyl derivative of a β -amino- α,β -unsaturated acid.²⁰⁸ Similarly, enamino esters react with benzoyl chloride to yield 6*H*-1,3-oxazines.²⁰⁹



Meier,²¹⁰ and Krantz and Hoppe²¹¹ obtained 6*H*-1,3-oxazin-6-one (**68**) by pyrolysis (650°C) of 3-ethoxycarbonylamino-2-propenal.²¹¹ It shows interesting properties, described in Section III,E.



According to Sasaki *et al.*,²¹² diphenylcyclopropanone reacts with *N*-iminopyridinium ylids on refluxing in benzene to produce 2,4,5-trisubstituted-6*H*-1,3-oxazine-6-one (**69**) [Eq. (54)]. Matsukubo and Kato²¹³ described the reaction of diphenylcyclopropanone and benzonitrile oxide through a hypothetical spiro intermediate to give **69** (R = Ph) in 40% yield [Eq. (55)].

²⁰⁴ E. Gore, M. F. Chasle, and A. Foucaud, *Tetrahedron* **28**, 5055 (1972).

²⁰⁵ F. Eiden and B. S. Nagar, *Naturwissenschaften* **50**, 403 (1963).

²⁰⁶ E. Buschmann and W. Steglich, *Angew. Chem.* **86**, 414 (1974).

²⁰⁷ W. Steglich, E. Buschmann, and O. Hollitzer, *Angew. Chem.* **86**, 594 (1974).

²⁰⁸ N. D. Bondarchuk, V. V. Mamot, L. A. Lazuhina, G. V. Petetskaya, and V. P. Kukhar, *Zh. Org. Khim.*, **10**, 735 (1974).

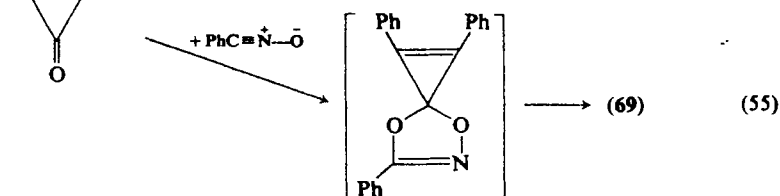
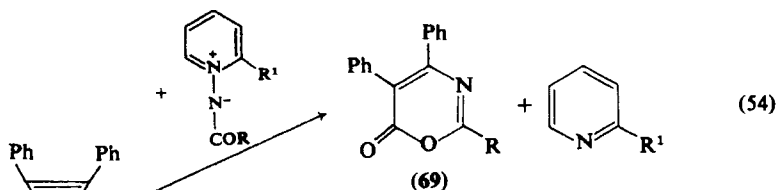
²⁰⁹ H. B. Kagan and Y-H. Suon, *Bull. Soc. Chim. Fr.*, 1819 (1966).

²¹⁰ G. Meier, *Angew. Chem., Int. Ed. Engl.* **13**, 425 (1974).

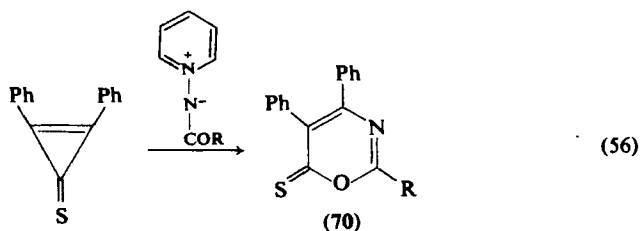
²¹¹ A. Krantz and B. Hoppe, *J. Am. Chem. Soc.* **97**, 6590 (1975).

²¹² T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.* **36**, 2451 (1971).

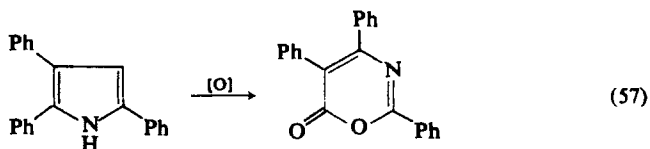
²¹³ H. Matsukubo and H. Kato, *J. Chem. Soc. Chem. Commun.*, 412 (1974).



Lown and Matsumoto²¹⁴ reacted diphenylcyclopropenethione with *N*-iminopyridinium ylids and obtained 2,4,5-trisubstituted-6*H*-1,3-oxazine-6-thione (70) [Eq. (56)].



Another interesting formation of 6*H*-1,3-oxazin-6-one derivatives by the oxidation of pyrrole derivatives was described by Sprio²¹⁵ [Eq. (57)] (see also Yee *et al.*²¹⁶).



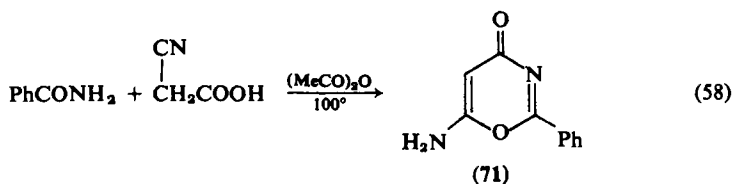
Ziegler and Steiner²¹⁷ described a general method for 6-amino-4-oxo-6*H*-1,3-oxazines (71) from amides and cyanoacetic acid [Eq. (58)].

²¹⁴ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **50** 584 (1972).

²¹⁵ V. Sprio, *Gazz. Chim. Ital.* **85**, 569 (1956).

²¹⁶ T. T. Yee, W. E. McEwen, and A. P. Wolf, *Tetrahedron Lett.*, 3115 (1965).

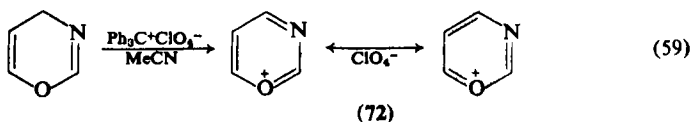
²¹⁷ E. Ziegler and E. Steiner, *Monatsh. Chem.* **96**, 212 (1965).



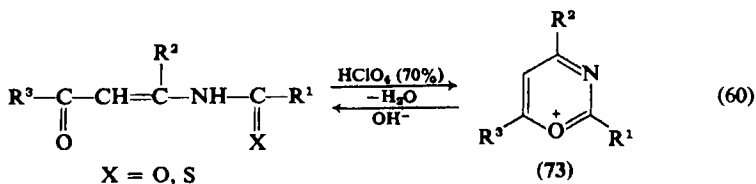
6*H*-1,3-Oxazines can be obtained by treating 1,3-oxazinium salts with hydrogen sulfide in basic medium⁴ (Section III,F,2,d).

K. 1,3-OXAZINIUM (3-AZAPYRYLIUM) SALTS

These cations (72) were first obtained by Wohl in 1901^{1,218} from 4*H*-1,3-oxazine and trityl perchlorate in acetonitrile [Eq. (59)]. Later



Schmidt *et al.*²¹⁹ cyclized β -acylaminocarbonyl compounds with perchloric acid to obtain 73 [Eq. (60)], in ca. 60% yield. The ring is opened in alkali.



Schmidt⁴ also described two possible 1,4-polar cycloadditions (Fig. 4, a and b) leading to 1,3-oxazinium salts [Eq. (61)] similar to

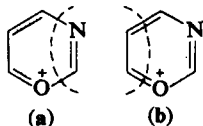
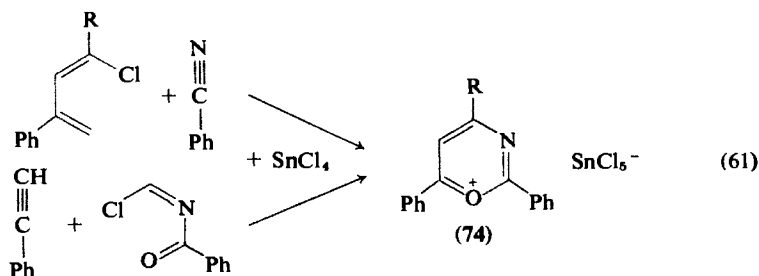


FIG. 4. Diagram of 1,4-polar cycloaddition to form 1,3-oxazinium salts.

²¹⁸ A. Wohl, *Chem. Ber.* **34**, 1914 (1901).

²¹⁹ R. R. Schmidt, D. Schwillie, and S. Sommer, *Ann. Chem.* **723**, 111 (1969).



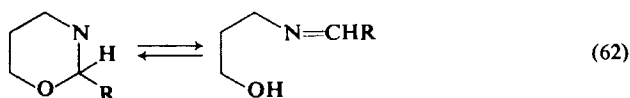
those in Eqs. (46) and (47). In method **a**, β -chlorovinylarylketones react with arylcarbonitriles in the presence of SnCl_4 to yield the 2,6-diaryl-1,3-oxazin-4-ium salts.²²⁰ In **b**, *N*-acylimidochlorides react with arylacetylenes in the presence of SnCl_4 to give 2,4,6-triaryl-1,3-oxazin-4-ium salts (**74**; $\text{R} = \text{aryl}$).²²⁰

III. Chemical Properties

A. TETRAHYDRO-1,3-OXAZINES

As indicated previously,¹ ring opening occurs readily with tetrahydro-1,3-oxazines. This property was recently reviewed,³⁷ and the review includes a description of the formation of 3-amino-2-nitropropanol and of 2-amino-1-nitro compounds, hydrolysis and degradation products, respectively, of the tetrahydro-1,3-oxazines.

Meyers *et al.*^{221,222} showed that tetrahydro-1,3-oxazines exist in tautomeric ring-chain forms [Eq. (62)]. When a 5,6-dihydro-1,3-oxazine is reduced to a tetrahydro-1,3-oxazine, some 3-aminoalcohol can also be formed through the reduction of the open-chain imino form [cf. Eq. (62)]. To avoid this the reduction should be carried out with sodium borohydride at -40°C .



²²⁰ R. R. Schmidt, *Chem. Ber.* **98**, 334 (1965).

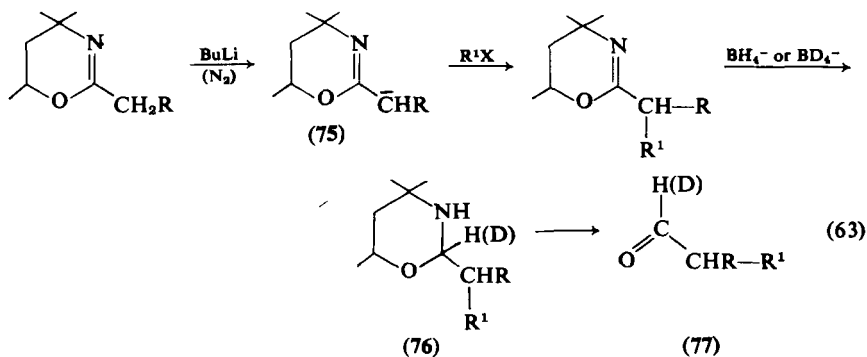
²²¹ A. I. Meyers and A. Nabeya, *J. Chem. Soc., Chem. Commun.*, 1163 (1967).

²²² A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovel'sky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.* **38** 36 (1972).

1. *Synthesis of Aldehydes*

The ring opening of tetrahydro-1,3-oxazines to aldehydes has recently found wide application through the work of Meyers.^{2,3} 2-Alkylidene-tetrahydro-1,3-oxazines, prepared from the readily available 5,6-dihydro-4*H*-1,3-oxazines, possess strong nucleophilic properties and can react with alkyl halides and carbonyl compounds. The derivatives so obtained can be reduced to tetrahydro-1,3-oxazines, and through ring opening the latter can furnish acyclic, alicyclic, and α,β -unsaturated aldehydes and their C-1 deuterated derivatives.^{221-223,226}

The first step consists of the formation of lithio salts by treatment of 5,6-dihydrooxazines with phenyl-, *n*-butyl-, or *t*-butyllithium in tetrahydrofuran at -78° .^{1,3,22,223} The lithio salts can readily be alkylated by alkyl halides to **75**, and the product can be reduced with aqueous sodium borohydride (or borodeuteride) at pH 7 in tetrahydrofuran-ethanol-water at -35° to -45°C to tetrahydro-1,3-oxazines (**76**) in quantitative yield. The latter^{224-228,236} on hydrolysis with aqueous oxalic acid give aldehydes (**77**) [Eq. (63)].



²²³ A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.* **91**, 763 (1969).

²²⁴ A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, 3715 (1970).

²²⁵ A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Politzer, *J. Am. Chem. Soc.* **91**, 764 (1969).

²²⁶ A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *J. Am. Chem. Soc.* **91**, 765 (1969).

²²⁷ H. W. Adickes, I. R. Politzer, and A. I. Meyers, *J. Am. Chem. Soc.* **91**, 2155 (1969).

²²⁸ A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 1783 (1969).

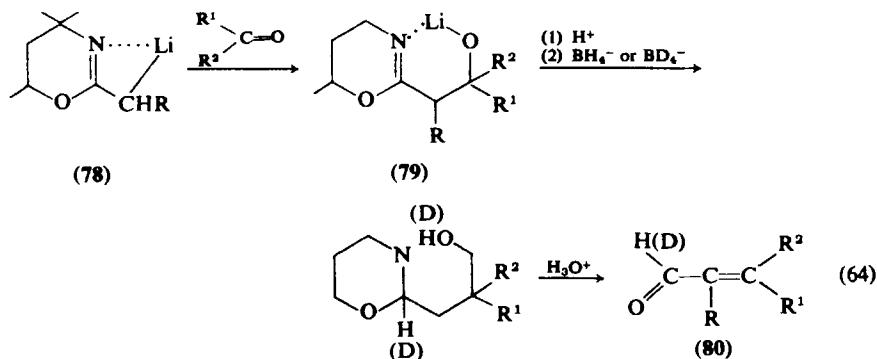
²²⁹ A. I. Meyers and N. Nazarenko, *J. Am. Chem. Soc.* **94**, 3243 (1972).

²³⁰ A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).

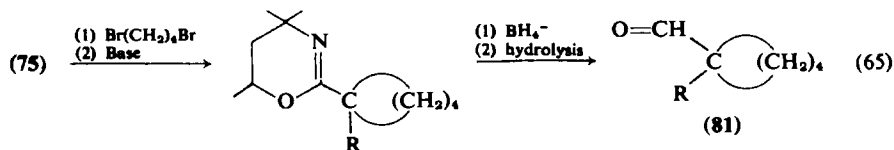
²³¹ G. R. Malone and A. I. Meyers, *J. Org. Chem.* **39**, 713 (1974).

²³² A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 4809 (1969).

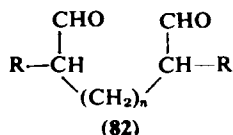
The lithio salt can react with various electrophiles, as in the reaction of **78** with ketones to yield **79**, which after reduction and hydrolysis furnish unsaturated aldehydes (**80**)²²⁵ [Eq. (64)].



Further development of the reaction leads to cycloalkanecarboxaldehydes.^{222, 226} The carbanion (**75**) can react with α,ω -dibromoalkanes, with further base, to obtain the product **81** after reduction and hydrolysis [Eq. (65)]. From 1 mole of the dibromoalkanes and 2 moles of



lithium salt (**75**) followed by borohydride and acid hydrolysis, dialdehydes (**82**) were formed.²²⁴



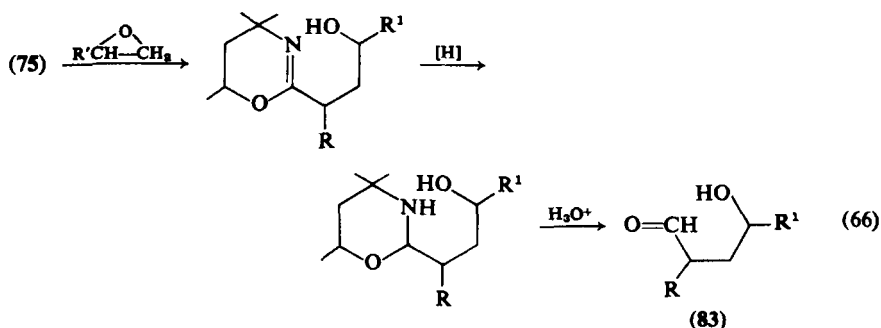
γ -Hydroxyaldehydes (**83**) can be obtained similarly from 5,6-dihydro-4*H*-1,3-oxazines and epoxides²²⁷ [Eq. (66)].

²²³ A. I. Meyers and A. C. Kovelesky, *J. Am. Chem. Soc.* **91**, 5887 (1969).

²²⁴ A. I. Meyers and E. M. Smith, *Tetrahedron Lett.*, 4355 (1970).

²²⁵ A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Am. Chem. Soc.* **93**, 2314 (1971).

²²⁶ A. I. Meyers and E. M. Smith, *J. Am. Chem. Soc.* **92**, 1084 (1970).

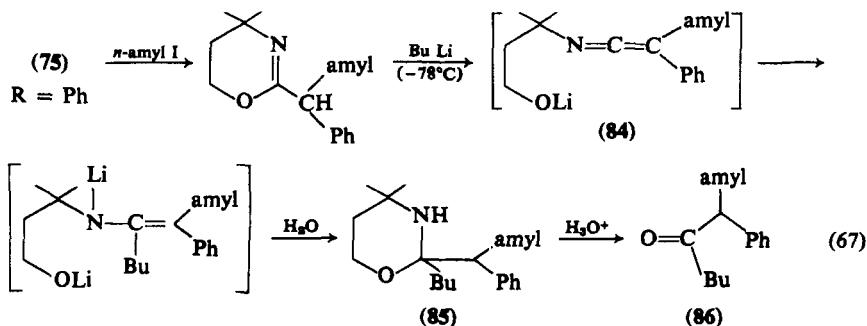


The scope of the synthesis was extended by using a 2-vinyloxazine, which led to the formation of propionaldehyde derivatives.²²⁷ Another modification of the aldehyde synthesis started with quaternary salts that were treated with sodium hydride, alkylated, then reduced with sodium borohydride to tetrahydro-1,3-oxazines.²²⁹

Another conversion of 5,6-dihydro-4*H*-1,3-oxazine derivatives into tetrahydro-1,3-oxazines treats the former with butyllithium in ether or tetrahydrofuran at -78°C .²³⁰ This method was applied to some 5,6-dihydro compounds that resisted borohydride such as β -keto derivatives (substituted in position 2) of 5,6-dihydrooxazines.²³¹

2. Synthesis of Ketones

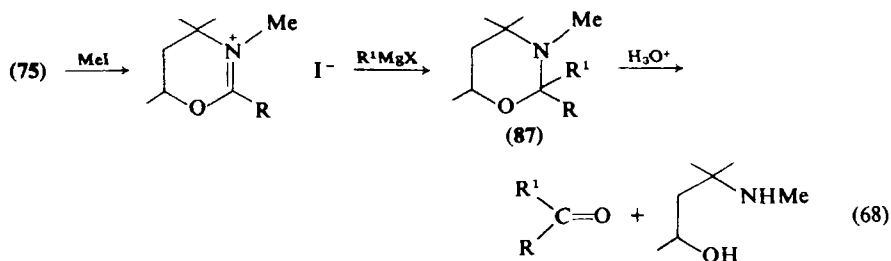
Ketones are produced from tetrahydrooxazines with branched substituents in position 2,²³²⁻²³⁵ as summarized in Eq. (67).²³⁴ Ketenimine



intermediate (84) leads to substituted ketones by addition of organo-metallics.

Another synthesis of tetrahydro-1,3-oxazines with two substituents in

position 2²³⁶⁻²⁴⁰ is based on the increased electrophilicity of the C=N bond on quaternization. Addition of organometallics such as organolithium compounds and Grignard reagents to these occurs at room temperature [Eq. (68)].



Preparative details for passing from dihydro- to tetrahydro-1,3-oxazines followed by ring opening have been given.^{241,242} The methods have been used to synthesize systems related to natural products²⁴³ including those with a pyrrole ring.²⁴⁴⁻²⁴⁶

B. 5,6-DIHYDRO-4H-1,3-OXAZINES

1. Hydrolysis

5,6-Dihydro-1,3-oxazines can be hydrolyzed and ring opened as described previously.¹ The reaction was used to obtain benzoylhydroxylysine and pseudoephedrine derivatives.⁴

a. *Synthesis of Aldehydes, Ketones, and Isocyanates.* Meyers *et al.*²⁴⁷ prepared aldehydes and ketones without using tetrahydro-1,3-oxazines.

²³⁷ A. I. Meyers and E. M. Smith, *J. Org. Chem.* **37**, 4289 (1972).

²³⁸ A. I. Meyers and N. Nazarenko, *J. Org. Chem.* **38**, 175 (1973).

²³⁹ A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.* **38**, 2199 (1973).

²⁴⁰ G. R. Malone and A. I. Meyers, *J. Org. Chem.* **39**, 623 (1974).

²⁴¹ J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, *Org. Prep. Proc.* **1**, 193 (1969).

²⁴² A. C. Kovelesky and A. I. Meyers, *Org. Prep. Proc.* **1**, 213 (1969).

²⁴³ A. I. Meyers and E. W. Collington, *Tetrahedron* **27**, 5979 (1971).

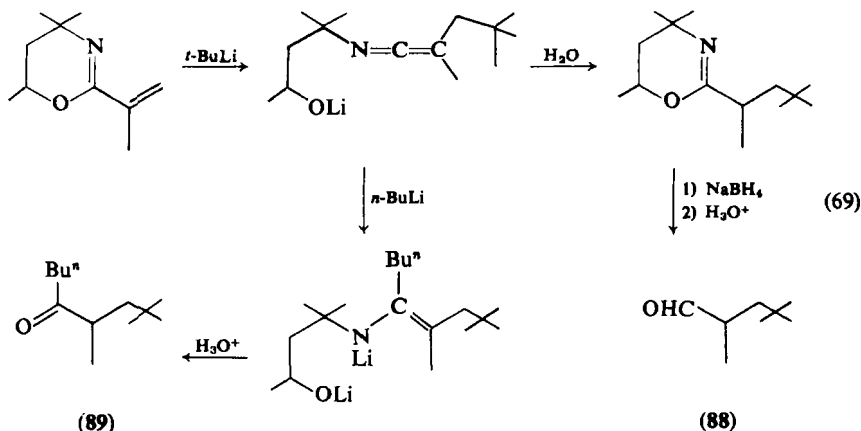
²⁴⁴ A. I. Meyers, T. A. Narwid, and E. W. Collington, *J. Heterocycl. Chem.* **8**, 875 (1971).

²⁴⁵ A. I. Meyers and R. L. Nolen, E. W. Collington, T. A. Narwid, and R. C. Strickland, *J. Org. Chem.* **38**, 1974 (1973).

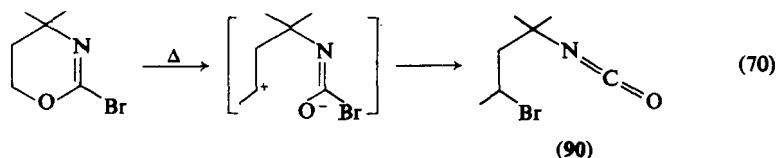
²⁴⁶ T. A. Narwid and A. I. Meyers, *J. Org. Chem.* **39**, 2572 (1974).

²⁴⁷ A. I. Meyers, A. C. Kovelesky, and A. F. Jurjevich, *J. Org. Chem.* **38**, 2136 (1973).

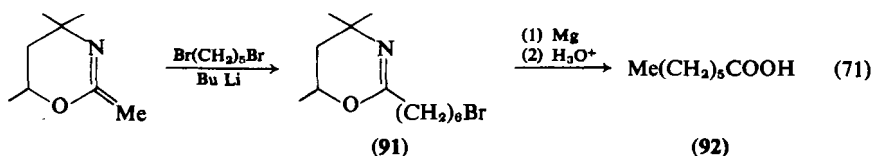
The reactions [Eq. (69)] yield an aldehyde (88) by direct hydrolysis or a ketone (89) through the formation of a ketenimine.



Isocyanates (90) were formed by pyrolysis of 2-bromo-5,6-dihydro-1,3-oxazine²²⁸ [Eq. (70)].

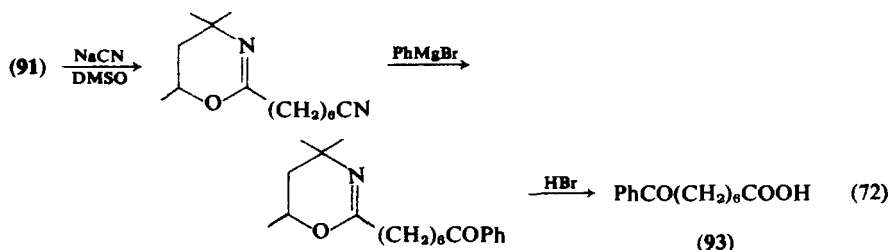


b. *Synthesis of Acids.* Hydrolysis of 5,6-dihydro-4*H*-1,3-oxazines (91) can also yield carboxylic acids (92) according to Eq. (71).



The 5,6-dihydrooxazine system is inert toward Grignard reagents^{236,248} unless quaternized. Consequently, the dihydro system represents a protecting group for reactions involving Grignard reagents. This property allows the synthesis of both aliphatic and aromatic acyl carboxylic acids (93) from appropriately substituted dihydro-1,3-oxazines²⁴⁸ [Eq. (72)].

²⁴⁸ A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Am. Chem. Soc.* **91**, 5886 (1969).



2-Chloromethyl-5,6-dihydro-1,3-oxazines react with aryl Grignard reagents, giving ultimately an arylacetic acid.²⁴⁹ Quaternary salts of 5,6-dihydro compounds also furnish carboxylic acids.²⁴⁰

2. Thermolysis

Thermolysis of 5,6-dihydro-1,3-oxazines, e.g. (36), gave *N*-allylamides ($\text{RCONHCH}_2\text{CH}=\text{CH}_2$) in good yield.^{152,158}

3. Addition

Although the $\text{C}=\text{N}$ double bond is not very active, some additions have been recorded; for instance, the addition of epoxides.^{15,59,227}

Michael addition of substituted electrophilic olefins to the activated 2-substituent yields pyrrolooxazines on cyclization.²⁴⁴⁻²⁴⁶

5,6-Dihydro-1,3-oxazines are usually reduced by borohydrides^{2,3}; reasons for some failures have been discussed.²²⁹ Catalytic hydrogenation led to ring opening.⁵⁸

4. Tautomerism

As pointed out previously (Section II,B,1,e), 2-amino-5,6-dihydro-4*H*-1,3-oxazines are tautomeric with 2-imino-tetrahydro-1,3-oxazines¹²⁵ [Eq. (23)].

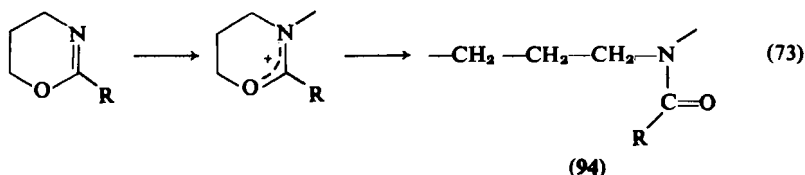
5. Polymerization

The interesting ability of 5,6-dihydro-4*H*-1,3-oxazine to take part in a new type of copolymerization, without catalyst, involves the combination of a cationic and an anionic monomer.²⁵⁰ The formation of the

²⁴⁹ G. R. Malone and A. I. Meyers, *J. Org. Chem.* **39**, 618 (1974).

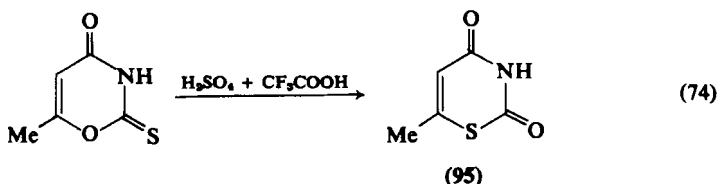
²⁵⁰ T. Saegusa, Y. Nagura, and S. Kabayashi, *Macromolecules* **6**, 495 (1973); T. Saegusa, *Int. Symp. Polymerization of Heterocycles (Ring-Opening)*, IUPAC, 1st, 1975, *Abstr.*, p. 21.

monomeric unit (94) through an intermediate cation is shown in Eq. (73).



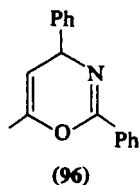
C. 3,4-DIHYDRO-2H-1,3-OXAZINES

4-Oxo-2-thiono-3,4-dihydro-1,3-oxazine rearranges¹⁸⁸ into the 2,4-dioxo-1,3-thiazine (95) [Eq. (74)].

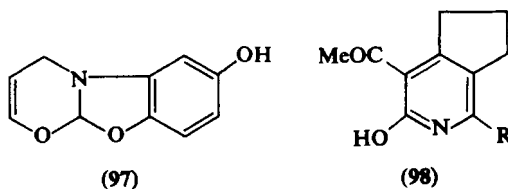


D. 4H-1,3-OXAZINES

4H-1,3-Oxazines react with trityl perchlorate to yield, for example, the 2,4,6-triphenyl derivative (96) which is readily hydrolyzed to a



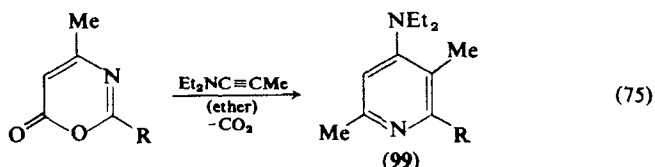
β -acylaminocarbonyl compound [Eq. (60)].²¹⁹⁻²²⁰ 4H-1,3-Oxazine also reacts with *p*-benzoquinone yielding 97.²⁰⁸ Kato *et al.*²⁵¹ described the addition of an enamine to give a pyridine derivative (98).



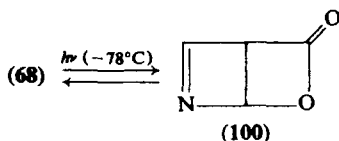
²⁵¹ T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles* 3, 293 (1975) [*CA* 83, 97165 (1975)].

E. 6H-1,3-OXAZINES

6H-1,3-Oxazin-6-one afford novel synthetic possibilities. Ring opening of their 5-methoxycarbonyl derivatives by alcoholic potassium hydroxide yielded aminomethylene derivatives of malonic ester.²⁵² Ammonia in ethanol converted 2,4,5-triphenyl-6H-1,3-oxazin-6-one into the corresponding pyrimidone.²⁵³ 6H-1,3-Oxazin-6-ones react exothermically with diethylpropynylamine to yield pyridine derivatives (99) [Eq. (75)].²⁵⁴ Similarly the reaction with enamines yields pyridines.



6H-1,3-Oxazin-6-one (68) is readily hydrolyzed to an open-chain product. It is isomerized by UV irradiation to the bicycle with fused four-membered rings (100), which on heating reverted to 68.^{210,211} Prolonged irradiation decomposed the substance into hydrogen cyanide, carbon dioxide, and acetylene.²¹¹



F. 1,3-OXAZINIUM (3-AZAPYRYLIUM) SALTS

The properties of 1,3-oxazinium salts are similar to those of pyrylium salts.^{4,194,219,255-259} 1,3-Oxazinium salts are intermediates for the synthesis of derivatives of pyrazole, isoxazole, pyridine, pyrimidine, quinoline, isoquinoline, chromene, benzopyrylium salts, butadiene, etc.⁴

²⁵² G. Lo Vecchio and M. Gattuso, *Atti Soc. Peloritana Sci. Fis. Mat. Nat.* **14**, 439 (1968) [*CA* **74**, 3538 (1971)].

²⁵³ V. Sprio, *Ric. Sci., Parte 2, Sez. B* [2] **4**, 585 (1964) [*Chem. Zentr.* **8**, 1144 (1967)].

²⁵⁴ W. Steglich, E. Buschmann, and O. Hollitzer, *Angew. Chem.* **86**, 596 (1974).

²⁵⁵ K. Dimroth, *Angew. Chem.* **72**, 331 (1960).

²⁵⁶ W. Schroth, *Z. Chem.* **4**, 281 (1964).

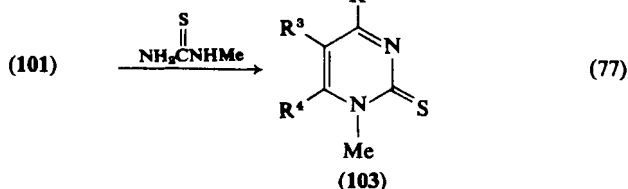
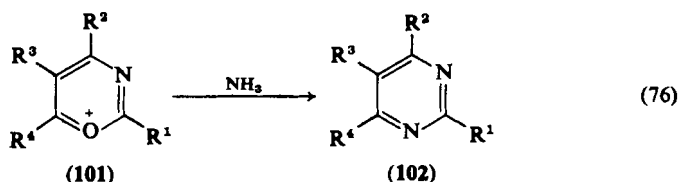
²⁵⁷ R. R. Schmidt, *Tetrahedron Lett.*, 4357 (1965).

²⁵⁸ R. R. Schmidt and D. Schwille, *Chem. Ber.* **102**, 269 (1969).

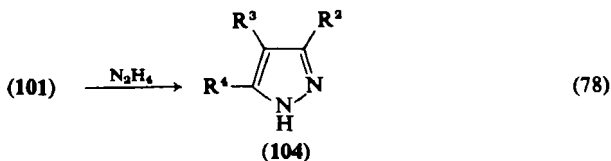
²⁵⁹ R. R. Schmidt, D. Schwille, and H. Wolf, *Chem. Ber.* **103**, 2760 (1970).

1. *Ring Opening and Closure*

a. *Reactions with Water and Nucleophiles Containing Nitrogen.*⁴ Through nucleophilic attack by water at position 6 the ring of **101** can be opened and the intermediate attacked by a nitrogen nucleophile, such as ammonia, urea, or their derivatives. Ring closure to pyrimidine derivatives **102** and **103** follows⁴ [Eqs. (76) and (77)].



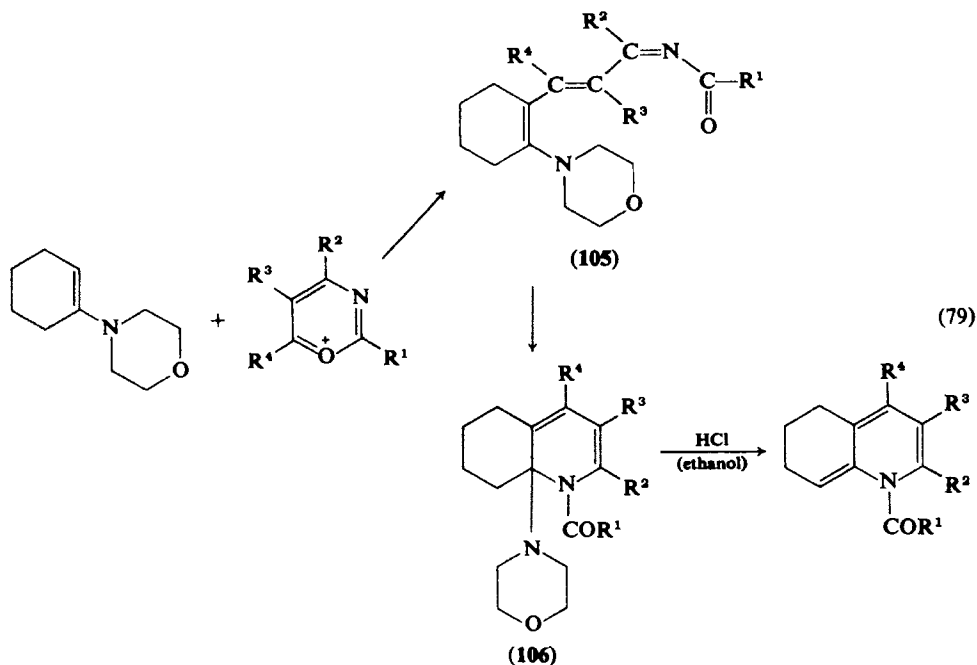
Hydrazine and hydroxylamine give pyrazoles (**104**) and isoxazoles, respectively, as shown in Eq. (78).



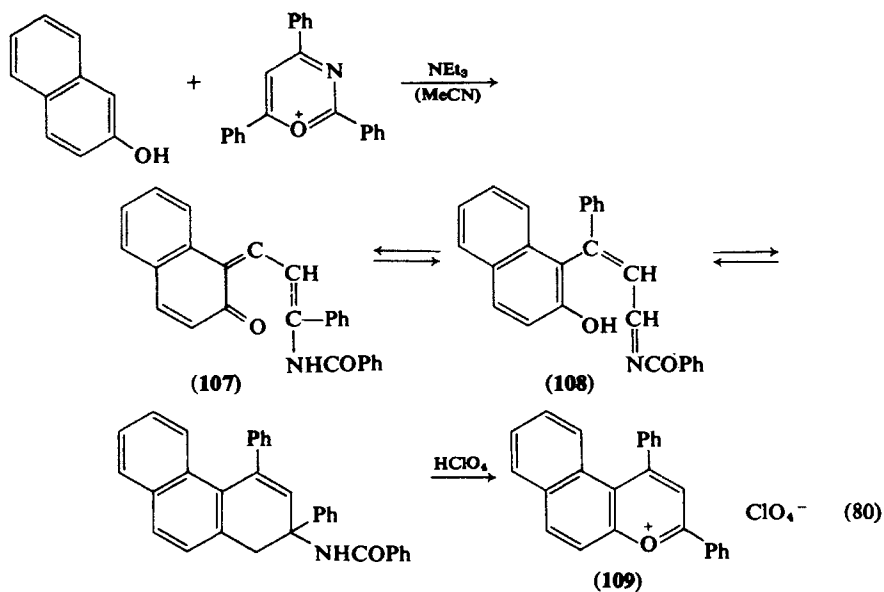
Enamines (e.g., morpholinocyclohexene) react with an oxazinium ion yielding two products—a butadiene analog (**105**) and a tetrahydroquinoline (**106**),^{4,194} as shown in Eq. (79).

2. *Reactions with Nucleophilic Carbon Compounds*

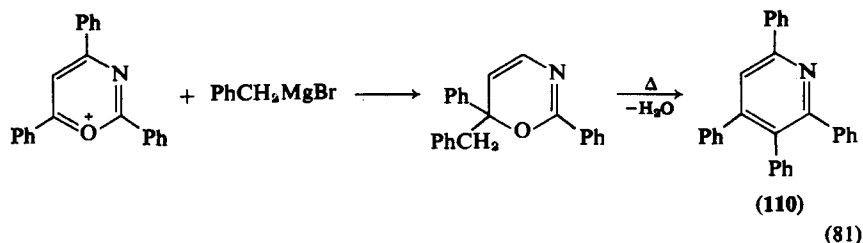
a. *Reactions with Phenols.*⁴ Nucleophilic attack of phenoxide at position 6 of the 1,3-oxazinium ion yields a benzopyrylium salt (**109**)



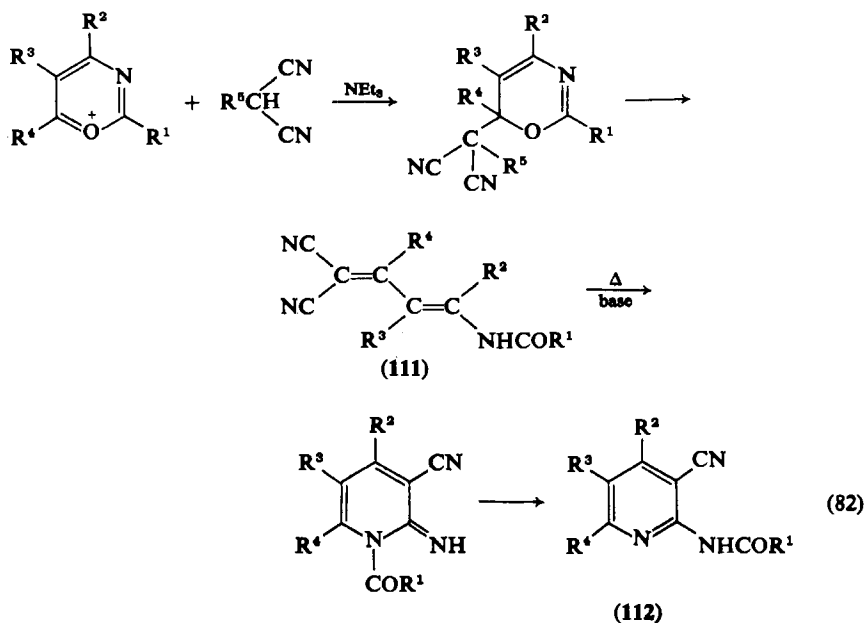
through intermediates **107** and **108** [Eq. (80)]. Intermediates **107** and **108** may be isolated depending on the phenol used.²²⁵



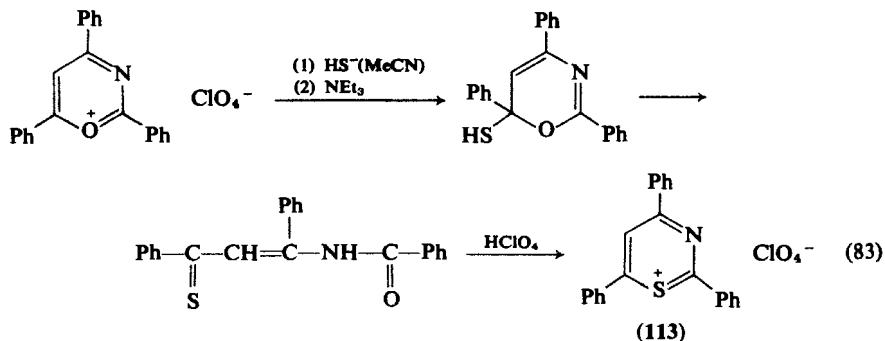
b. *Reactions with Grignard Reagents.*⁴ Pyridines, e.g., **110**, are formed by nucleophilic attack of a benzyl Grignard reagent [Eq. (81)].



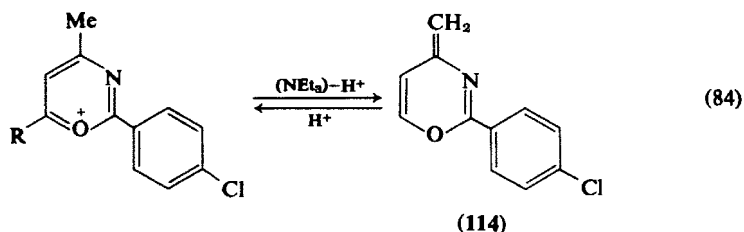
c. *Reactions with C-H Acidic Compounds.* Monosubstituted malonitriles with oxazinium salts in an anhydrous basic medium yield *cis*- and *trans*-butadienes (**111**), which on heating cyclize to pyridines (**112**)^{4,194,219} [Eq. (82)].



d. *Reactions with Nucleophilic Sulfur Compounds.* The hydrogen sulfide anion with an oxazinium salt yields eventually the 1,3-thiazinium perchlorate (**113**)⁴ [Eq. (83)].



e. *Proton Elimination.* Aryl-substituted 1,3-oxazinium salts are electrophilic and their electron deficiency can be compensated by elimination of a proton from an α -C—H bond. With bases the 4*H*-1,3-oxazine (114) can be formed⁴ [Eq. (84)]. The oxazinium salt is regenerated with acids.



f. *Oxazinyl Anion.* Recently, Schmidt²⁶⁰ studied the formation of the oxazinyl anion through the action of strong bases on 4*H*-1,3-oxazines [Eq. (85)]. The latter loses a proton to yield the anion (115), which, in turn, is in equilibrium with oxazabicyclo[3,1,0]hexenyl anions (116a, b, and c). The oxazinyl anion with an antiaromatic octet of π -electrons is highly reactive.

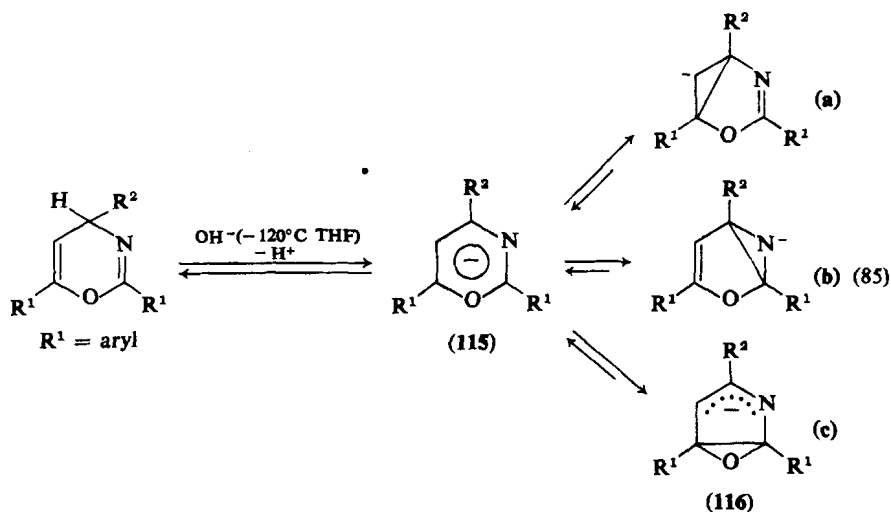
IV. Conformation

Investigations of the conformational analysis of 5-alkyl-5-nitro-tetrahydro-1,3-oxazines by dipole moments¹ have been extended to derivatives with various substituents in positions 3 and 5.^{261,262} They

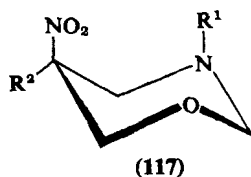
²⁶⁰ R. R. Schmidt, *Angew. Chem.* **87**, 603 (1975).

²⁶¹ T. Urbański, *Zh. Vses. Khim. Ova.* **7**, 396 (1962).

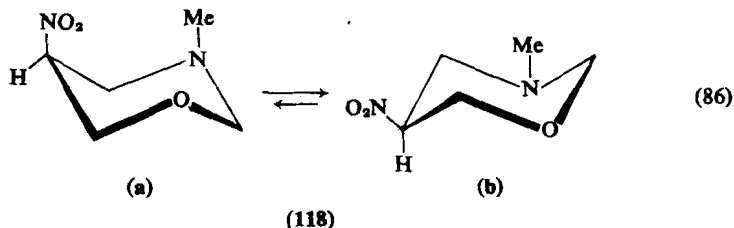
²⁶² T. Urbański, D. Gürne, R. Koliński, H. Piotrowska, A. Jończyk, B. Serafin, M. Szretter-Szmid, and M. Witanowski, *Tetrahedron* **20**, Suppl. 1, 195 (1964).



confirmed the previous finding of the chair form with axial 5-nitro and equatorial 5-alkyl and 3-cyclohexyl groups. A *t*-butyl was equatorial, but all primary alkyl groups occupy the axial position (117).²⁶² A possible explanation for the preference of both 5-NO₂ and 3-alkyl to be axial was given^{37,263} in terms of a 1,3-attractive interaction, the nitro group being the electron acceptor, and the alkyls or aralkyls the electron donors.

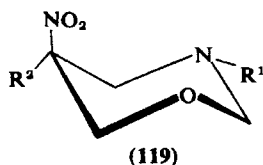


When hydrogen was in position 5, an equilibrium between axial NO₂-axial *N*-methyl and equatorial NO₂-equatorial *N*-methyl was suggested on the basis of dipole moment measurement [Eq. (86)].



²⁶³ T. Urbański, *J. Sci. Ind. Res.* 33, 124 (1974).

These findings have been confirmed by NMR analysis.²⁶⁴⁻²⁶⁶ Allingham and Crabb *et al.*²⁶⁷ agreed with these conclusions on the basis of NMR examination, but they did not rule out a certain amount of form 119 existing in equilibrium with 117 due to nitrogen inversion.



Eliel *et al.*²⁶⁸ seem to confirm the observation that the nitro group in this type of heterocyclic system is preferred in the axial position. Katritzky *et al.*²⁶⁹⁻²⁷¹ have found on the basis of dipole moment measurements that tetrahydro-1,3-oxazines without a 5-nitro group have *N*-alkyl in the preferred equatorial position, although the axial $N\text{-CH}_3$ and $\text{-C}_2\text{H}_5$ are important minor contributors (42 and 32%, respectively).

Since the advent of NMR as a tool for conformational analysis, a number of papers have been dedicated to conformation of tetrahydro-1,3-oxazine in addition to those mentioned above. Nevertheless, conclusions based on coupling constant measurements are valid only for closely related compounds.²⁶⁹

Inversion at the nitrogen atom, mentioned already,²⁶⁷ was also discussed by Italian,¹⁶ French,¹⁷ and Soviet authors²⁷² on the basis of NMR examination of derivatives of tetrahydro-1,3-oxazine. In another series of papers,^{32,33,273} Soviet authors concluded from NMR, dipole

²⁶⁴ D. Gürne, L. Stefaniak, T. Urbański, and M. Witanowski, *Tetrahedron* **20**, Suppl. 1, 211 (1964).

²⁶⁵ R. C. Cookson and T. A. Crabb, *Tetrahedron* **24**, 2385 (1968).

²⁶⁶ P. J. Chivers and T. A. Crabb, *Tetrahedron* **26**, 3389 (1970).

²⁶⁷ Y. Allingham, R. C. Cookson, T. A. Crabb, and S. Very, *Tetrahedron* **24**, 4625 (1968).

²⁶⁸ M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, and E. L. Eliel, *J. Am. Chem. Soc.* **98**, 956 (1976).

²⁶⁹ P. J. Halls, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc. B*, 132; (1971).

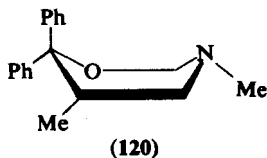
²⁷⁰ R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, *J. Chem. Soc., Chem. Commun.*, 673 (1972).

²⁷¹ I. G. Ferguson, A. R. Katritzky, and D. M. Read, *J. Chem. Soc., Chem. Commun.*, 255 (1975).

²⁷² Yu. E. Kazantsev, I. P. Boiko, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and B. V. Unkovskii, *Zh. Org. Khim.* **9**, 2597 (1973).

²⁷³ Yu. Yu. Samitov, O. I. Zhuk, B. V. Unkovskii, I. P. Boiko, and Yu. F. Malina, *Zh. Org. Khim.* **9**, 201 (1973).

moments, and magnetic susceptibilities that three types of conformation of tetrahydro-1,3-oxazine exist—chair, boat, and twist boat. Tetra-substituted derivatives present a particular interest: 3,5-dimethyl-6,6-diphenyl (**120**) and 3,4,4,6-tetramethyl-6-phenyl have a preferred boat conformation.



Solvent effects can also play an important part in determining the preferred conformation.

Infrared spectra and dipole moments led to the conclusion that the N-H in tetrahydro-1,3-oxazines is predominantly axial.²⁷⁰

Examination of CH-NH coupling constants at low temperature indicated that the N-H axial conformation is the dominant or sole conformation and that an *N*-methyl substituent is in part axial.²⁵ The latter finding was in agreement with that from dipole moment measurements.²⁶ At different temperatures (30°–75°C),^{17,18} NMR gave the thermodynamic functions for the activation energy to ring inversion: $\Delta G^\ddagger = 10.8$ kcal/mole, $\Delta H^\ddagger = 10.4$ kcal/mole, $\Delta S^\ddagger = -0.5$ cal/mole/deg. Low-temperature NMR spectra of *N*-methyl and *N,C*-polymethyl derivatives of tetrahydro-1,3-oxazine permitted Katritzky *et al.*²⁷¹ to calculate conformational equilibria and *N*-methyl inversion barriers. They found the free energy of activation for inversion $\Delta G^\ddagger = 6.8$ –7.6 kcal/mole. Direct integration of the two *N*-methyl peaks gave $\Delta G_{298}^\circ = 0.16$ kcal/mole, a figure close to that found earlier²⁶ from dipole moment measurements.

As noted in Section II,A,3, diastereoisomeric quaternary salts of 5-nitrotetrahydro-1,3-oxazines are formed through different conformations of substituents in position 3 [Eqs. (4) and (5)].⁶¹

The conformations of the 2-oxo-tetrahydro-1,3-oxazines obtained from phosgene and the isomeric 3-amino-2,3-diphenylpropanols were used by Fodor *et al.* as an ingenious criterion for the configurational determination of the aminopropanols.^{13,14} The erythro form yielded an oxazinone that showed optical activity 4–8 times stronger than that from the threo form.

Kurtev and co-workers²⁷⁴ examined the conformation of *trans*-4,5-diphenyltetrahydro-1,3-oxazin-2-one (**121**) by NMR. They concluded

²⁷⁴ A. S. Orahovats, S. M. Mishev, I. G. Pozharliev, and B. J. Kurtev, *Dokl. Bolg. Akad. Nauk* **26**, 1625 (1973) [*Ref. Zh.*, *Khim.* **14** Zh, 48 (1974)].

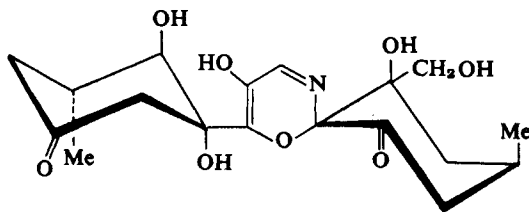
- ²⁷⁵ S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltivanger, and R. F. Bryan, *J. Am. Chem. Soc.* **94**, 1354 (1972).
²⁷⁶ S. M. Kupchan, Y. Komoda, G. J. Thomas, and H. P. J. Hintz, *J. Chem. Soc., Chem. Commun.*, 1065 (1972).
²⁷⁷ A. I. Meyers, C. C. Shaw, D. Horne, L. M. Trefonas, and R. J. Majeste, *Tetrahedron Lett.*, 1745 (1975).

and Calubrinol acetate, isolated by Wani *et al.*²⁷⁸ from *Calubrina texensis*. Maytenus macrolides are represented by formula 122; R is Me, Et, and *i*-Pr in Maytansine, Maytanprine, and Maytanbutine, respectively. Calubrinol differs from Maytansine only by the presence of an additional hydroxy group and this is acetylated in Calubrinol acetate.

Recently Kupchan *et al.*²⁷⁹ isolated two Maytansinoids: Maytanacine and Maytansinol. They differ from the previously described Maytansinoids by different substituents at C-3, both being without an amino acid residue at that position. Semisynthetic Maytansinoids have also been prepared by esterification of the 3-OH group of Maytansinol.

Corey and Bock²⁸⁰ designed a synthetic route to Maytansine, and obtained a fragment of the molecule containing the 1,3-oxazine ring.

Rice²⁸¹ isolated Leucogenenol, a metabolite of *Penicillium gilmanii*, and attributed to it the *spiro-2H-1,3-oxazine* structure (123). It is also found in bovine and human liver.²⁸²



(123)

2. Antitumor Activity

5-Nitrotetrahydro-1,3-oxazine derivatives show cytotoxic activity *in vitro*,^{283,284} and antitumor properties against subcutaneous tumors in mice.^{64,285} Compound 124 reduced tumors by 70%. The preparation of these compounds is covered by patents.⁴¹⁻⁴⁵

²⁷⁸ M. C. Wani, H. L. Taylor, and M. E. Wall, *J. Chem. Soc., Chem. Commun.*, 390 (1973).

²⁷⁹ S. M. Kupchan, A. R. Branfman, R. Alan, A. T. Sueden, A. K. Verma, R. G. Dailey, Y. Komoda, and Y. Nagao, *J. Am. Chem. Soc.* **97**, 5294 (1975).

²⁸⁰ E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 2643 (1975).

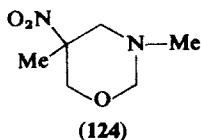
²⁸¹ F. A. H. Rice, *J. Chem. Soc. C*, 2599 (1971).

²⁸² F. A. H. Rice and B. Shaikh, *Biochem. J.* **116**, 709 (1970).

²⁸³ S. Slopek, H. Mordarska, M. Mordarski, T. Urbański, and D. Gürne, *Bull. Acad. Pol. Sci., Ser. Sci. Chim. Geol. Geogr.* **6**, 361 (1958).

²⁸⁴ Z. Eckstein, P. Gluziński, E. Grochowski, M. Mordarski, and T. Urbański, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **10**, 331 (1962).

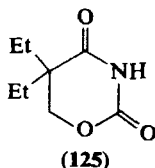
²⁸⁵ J. B. Chylińska, E. Grochowski, M. Mordarski, and T. Urbański, *Acta Unio Int. Cancrum* **20**, 118 (1964) [*CA* **61**, 8784 (1964)].



1,3-Oxazines without a nitro group have also been suggested as antitumor compounds.⁵⁸ Maytansinoids possess antileukemic and antitumor activity^{275-279,286} with the exception of Maytansinol.²⁷⁹

3. Various Activities

The only 1,3-oxazine so far with clinical application seems to be 5,5-diethyltetrahydro-1,3-oxazine-2,4-dione (**125**), known under trade names of Dioxone, Dietadion, and Diethadion. Its preparation was



described in patents.^{109,287} It is effective against barbiturate poisoning,²⁸⁷⁻²⁸⁹ as an analeptic and convulsant, stronger than Cardiazole,^{79,290-296} and in other ways.^{30,297} Action was found on the central

²⁸⁶ S. Renullard, L. I. Rebhun, G. A. Havic, and S. M. Kupchan, *Science* **189**, 1002 (1975) [*CA* **83**, 188257 (1975)].

²⁸⁷ Aspro-Nicholas Ltd., French Patent 1,575,005 [*CA* **72**, 111110 (1970)].

²⁸⁸ P. F. Mannaioni, *Clin. Ter.* **21**, 14 (1961) [*Chem. Zentr.*, 5756 (1962)].

²⁸⁹ F. B. Nicolis, C. Scocella, A. Ghisellini, G. Cenacchi, and G. Alberti, *Chemotherapia (Basel)* **4**, 485 (1962) [*Chem. Zentr.*, 20506 (1963)].

²⁹⁰ G. Scocella and A. Ghisellini, *Clin. Ter.* **21**, 19 (1961) [*Chem. Zentr.*, 5756 (1962)].

²⁹¹ G. Genacchi and G. Alberti, *Clin. Ter.* **21**, 44 (1961) [*Chem. Zentr.*, 5756 (1962)].

²⁹² G. Maffii, V. M. Dezulian, and B. Silvestrini, *J. Pharm. Pharmacol.* **13**, 244 (1961) [*Chem. Zentr.*, 5756 (1962)].

²⁹³ G. Maffii, G. Bianchi, P. Schiatti, and B. Silvestrini, *Brit. J. Pharmacol. Chemother.* **16**, 231 (1961) [*Chem. Zentr.*, 14773 (1963)].

²⁹⁴ G. Maffii and B. Silvestrini, *Farmaco, Ed. Sci.* **16**, 39 (1961).

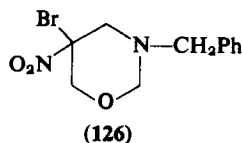
²⁹⁵ E. Fadiga, G. Maffii, and B. Silvestrini, *Boll. Soc. Ital. Biol. Sper.* **39**, 188 (1963).

²⁹⁶ E. Fadiga, T. Gessi, and G. Maffii, *Boll. Soc. Ital. Biol. Sper.* **39**, 191 (1963).

²⁹⁷ E. Fadiga, T. Gessi, and G. Maffii, *Arch. Sci. biol.* **18**, 149 (1964) [*Chem. Zentr.* **42**, 1523 (1966)].

nervous system,^{138,298,299} on blood pressure,^{18,73,132,175,219} and as an antiinflammatory agent.^{16,132}

Many patents describe the preparation of 1,3-oxazine derivatives as antibacterials and antifungals.^{21,22,27,69,81,87,89,90,129,300,301} Strong anti-protozoal activity of 5-bromo-5-nitrotetrahydro-1,3-oxazines, e.g., **126**, was also registered.^{302,303} *N*-Nitroso derivatives were found to be



molluscicides.⁶⁵⁻⁶⁷ Some oxazines are insecticides³⁰⁴ or herbicides.^{189,191} A few patents refer to the preparation of 1,3-oxazines with less defined medical use.^{305,306}

B. OTHER PRACTICAL APPLICATIONS

1,3-Oxazines with an olefinic substituent were suggested as polymerizable monomers.³⁰⁷⁻³⁰⁹ 1,3-Oxazines were claimed as plasticizers for cellulose acetate,³⁰⁹ tanning agents,¹⁹ and corrosion inhibitors.³¹⁰ *N*-Oxides of 1,3-oxazines were reported to be antioxidants and polymerization inhibitors.³⁴

²⁹⁸ D. M. Teller, C. J. Guinasso, S. C. Bell, and G. H. Duglas, U.S. Patent 3,817,994 [CA 81, 105531 (1974)].

²⁹⁹ F. Hoffmann-La Roche A.G., British Patent 1,047,110 (1966) [Chem. Zentr. 44, 1559 (1968)].

³⁰⁰ Norwich Pharmacal Co., British Patent 944,594 [Chem. Zentr. 36, 1783 (1966)].

³⁰¹ S. Ozaki, Japanese Patent 72 36742 [CA 77, 164,717 (1972)].

³⁰² B. Orłowska, M. Mordarski, D. Gürne, and T. Urbański, Arch. Immunol. Ther. Exp. 15, 404 (1967).

³⁰³ B. Orłowska, M. Mordarski, D. Gürne, and T. Urbański, Arch. Immunol. Ther. Exp. 15, 728 (1967).

³⁰⁴ R. L. McConnell and H. W. Coover (Eastman Kodak Co.) U.S. Patent 2,992,219 [Chem. Zentr. 15, 2025 (1964)].

³⁰⁵ C. Fauran, C. Douzon, G. Huguet, G. Raynaud, and Y. Bailly (Delalande S.A), Ger. Offen. 2,221,408 [CA 78, 58,435 (1973)].

³⁰⁶ M. Nakanishi, K. Arimura, and H. Aoi (Yotsitomi Seyaku), Japanese Patent 74 31993 [Ref. Zh. Khim. 80129P (1975)].

³⁰⁷ L. S. Luskin and P. La Roche de Bonneville (Rohm & Haas Co.), Ger. Offen. 1,067,437 [Chem. Zentr., 19785 (1963)].

³⁰⁸ W. F. Tousignant, W. E. Wallis, and T. Houtman (Dow Chemical Co.), U.S. Patent 3,030,339 [Chem. Zentr. 49, 2943 (1966)].

³⁰⁹ S. H. Metzger (Mobay Chemical Co.), U.S. Patent 3,479,351 [CA 72, 21699 (1970)].

³¹⁰ Chemische Werke Huels A.G., French Patent 1,585,475 [CA 74, 42365 (1971)].

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Medium-Large and Large π -Excessive Heteroannulenes

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I. Introduction

This review deals strictly with π heteromonocycles consisting of eight or more π centers and incorporating one or more π -excessive heteroatomic units. Bicyclic and polycyclic frames are not covered in this chapter unless they incorporate one or more π -excessive heteromonocyclic segments, each consisting of eight or more π centers.

Discussion of the subject matter centers primarily on such physico-chemical properties as are deemed indicative of π -electron mobility and the attendant development of "aromatic" or "antiaromatic" character. Although it is not entirely neglected, the description of synthetic procedure is limited for the most part to the crucial *final* step. It may also be well to note that, while a serious attempt has been made to provide as complete as possible coverage of the area, the main emphasis in this review is on proper representation rather than on exhaustive enumeration. Also, in order to achieve maximum effectiveness in the coverage of the literature, compounds belonging to a given size-class are described in terms of increasing molecular complexity rather than historical sequence.

II. Characterization and Discussion

A. GENERAL REMARKS

The relation of the heteroatomic lone pair to the common double bond in matters relating to π -electron mobility has long been accepted as a theoretically sound one.¹ Because of a general lack of synthetic methodology, however, representation in the area of π -excessive heterocycles was, until recently (early part of the past decade), limited to the long-known five-membered systems: pyrrole, furan, and thiophene. In fact, it was not until the late 1960's that well-developed synthetic procedures, such as (i) condensation with properly constructed Wittig reagents and (ii) the use of synthetic pericyclization, were successfully applied to the synthesis of the various substances now known.

Since this relatively "new" group of compounds is discussed in this review primarily in terms of the affinity of the lone pair to participate in cyclic delocalization, it would be instructive at this early stage briefly to review the structural demands imposed by π -electron mobility on medium-large and large monocyclic π ribbons. Bearing in mind that (i) conventional π delocalization derives maximum effectiveness when the various participating p centers are located on a planar frame and (ii) large-membered unrestricted monocycles possess highly flexible molecular frames with a natural tendency to distort from planarity, it would be best to analyze the situation in terms of the factors that primarily influence the transformation of the molecular frame from buckled to flat. In

¹ E. Hückel, *Z. Phys.* **76**, 628 (1932).

terms of key energy requirements this may simply be accomplished with the use of the well-known free energy relationship,

$$\Delta G_0(\text{B} \rightarrow \text{P}) = \Delta H_0^\pi + \Delta H_0^\sigma - T\Delta S_0 \quad (1)$$

Within the specified direction of change, i.e., buckled (B) to planar (P), ΔH_0^π [a negative quantity for $(4n + 2)$ π systems] denotes the stabilizing influence of electron delocalization, ΔH_0^σ (a positive quantity) represents the destabilizing effect of σ strain, and ΔS_0 (a negative quantity) describes the loss of molecular freedom attending the change from flexible to rigid. In general, a conformationally flexible cyclic π ribbon will satisfy the condition necessary for π -electron mobilization, i.e., $\Delta G_0(\text{B} \rightarrow \text{P}) < 0$, when the resulting stabilization due to ΔH_0^π is sufficiently pronounced to overcome the combined destabilization introduced by skeletal strain and reduced molecular mobility. Within the framework of simple Hückel theory, this may of course be accomplished only when the molecule is associated with $(4n + 2)$ π -electrons, for only then would the ΔH_0^π term be expected to have a stabilizing influence. Discussion of the many instances where Hückel theory has received firm and at times spectacular support among π carbocycles is beyond the scope of this review. Nonetheless, it might be instructive to review² a few basic $(4n + 2)$ π cases in terms of Eq. (1).

Benzene, being a skeletally rigid, strain-free, molecule containing $(4n + 2)$ π -electrons is a rare example of a case in which all three terms in Eq. (1) are stabilizing. For obvious reasons, as the molecule's ring size increases, the effects of ΔH_0^π and $\Delta H_0^\sigma - T\Delta S_0$ increasingly oppose one another with the former exerting controlling influence in such well-known *planar* delocalized members of the family of the 6π -tropylium cation, the 10π -cyclooctatetraenyl dianion (despite the destabilizing component introduced into ΔH_0^π by electron repulsion) and, finally, the highly strained [heavy contribution to ΔH_0^σ by angle strain (180°) and *peripheral* H-H repulsion] 10π -cyclononatetraenyl anion. The key transition of $\Delta G_0(\text{B} \rightarrow \text{P})$ from negative (stabilizing) to positive (destabilizing) occurs in the next higher 10π member of this all-cis family of carbocyclic π ribbons, i.e., cyclodeca-1,3,5,7,9-pentaene where the $\Delta H_0^\sigma - T\Delta S_0$ contribution assumes controlling influence in Eq. (1) leading to a heavily buckled π -localized frame. In the larger rings the angle strain contribution to ΔH_0^σ may be significantly reduced by the proper introduction of trans bonds, but the term continues to play an important role in Eq. (1) due to the development of *in-cavity* H-H repulsion. Finally, when the size of the π ribbon is increased to the point where its cavity is sufficiently

² For a brief but timely review on the subject see F. Sondheimer, *Chimia* **28**, 163 (1974).

large to accommodate two or more "inner" protons, the contribution of ΔH_0° in Eq. (1) drops significantly, but now the $T\Delta S_0$ term assumes added importance since the increased molecular size renders the molecule more flexible. The flexibility of a large cyclic π ribbon may, of course, be significantly reduced through bridging or by judicious replacement of one or more of its double bonds with triple bonds. In fact, it is only in such "restricted"³ systems, possessing rigidly flat π frames, that one might reasonably expect to observe the development of *anti-aromatic* ($4n - \pi$) delocalization despite its association with a destabilizing ΔH_0° term in Eq. (1).

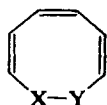
The views expressed in this brief introductory section concerning the development of delocalization in cyclic π ribbons are certainly not new. Nonetheless, the approach followed here, i.e., the separation of the major contributing factors in terms of Eq. (1), does appear to offer certain practical advantages over some of the more conventional descriptions of the subject.

B. MEDIUM-LARGE FRAMES; SYSTEMS CONTAINING EIGHT TO TWELVE π CENTERS

1. Systems with Eight π Centers

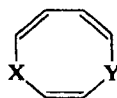
This family of π -excessive heterocycles whose members are isocyclic with cyclooctatetraene has been studied in considerable detail and is currently known in parent as well as variously benzoannulated forms.

a. *Parent Diheterocins*. These bis π -excessive diheteromonocycles are formally iso- π -electronic with the dianion of cyclooctatetraene, a well-documented aromatic system, and may exist in one of the two isomeric forms shown in **1** and **1'**.



(1)

- a: X = Y = NH
- b: X = Y = O
- c: X = Y = S
- d: X = NH, Y = O
- e: X = NH, Y = S
- f: X = O, Y = S



(1')

³ The term restricted is employed here to distinguish this system from annulated, dehydro, and bridged members of the family.

The system's 10π -electron potential was recognized in a review published⁴ some 17 years ago where it was further stated that of the two position isomers only the 1,4-variant (**1'**) might be expected to be aromatic. The reason offered for this prediction, i.e., that the 1,2-isomer (**1**) would not be endowed with a delocalized frame, was that the presence of two directly linked π -excessive heteroatoms would lead to an arrangement where "the number of bonding MO's is insufficient to contain all the p electrons."⁴ This analysis is basically a sound one as it appears to draw from the fact that the close proximity of the two sets of lone pairs in **1** must lead to strong, largely localized, interaction with consequent delivery of 2 of the 4 heteroatomic electrons into a predominantly antibonding MO level.

In other work,⁵ a direct comparison of the HMO delocalization energies of 1,4-isomers (**1'b** and **c**) calculated with the use of heteroatom parameters, $\alpha_o = \alpha + 2\beta$ and $\alpha_g = \alpha + \beta$, with the strain energies estimated for the hypothetical planar forms, revealed the latter to dominate in each case, thus leading to the conclusion that neither of these diheteromonocycles would possess a planar delocalized frame. In addition, it was shown that for the more weakly electronegative heteroatomic units, such as S and NH, the 1,2-isomer ought to possess a slightly lower π -binding energy than the 1,4 counterpart. The theoretical expectation of a nonaromatic 1,4-dithiocin (**1'c**) has recently gained strong support from the results of a more sophisticated HMO treatment, making proper use of reference structures, which show the system to be devoid of resonance stabilization.⁶

The theoretical predictions noted above concerning the 1,4-diheterocins were convincingly realized experimentally in work dealing with the parent system. Synthetic entry into a variety of "unrestricted" prototypes [**2a**,⁷ **2(b-d)**]⁸ was uniformly gained by subjecting properly structured *syn*-diheterotricycles of general formula **3** to thermally induced $2\sigma \rightarrow 2\pi$ retroelectrocyclization as shown in Scheme 1. A similar procedure also led to the synthesis of a number of substituted 1,4-homo-hetero[8]annulenes, (**4a-e**),⁹ although the method has yet to be applied to the synthesis of mixed diheterocins, such as **1'd-f**, which do not appear to be known. Attempts to prepare the parent 1,4-dithiocin (**1'c**)

⁴ M. E. Vol'pin, *Russ. Chem. Rev.* **29**, 129 (1960).

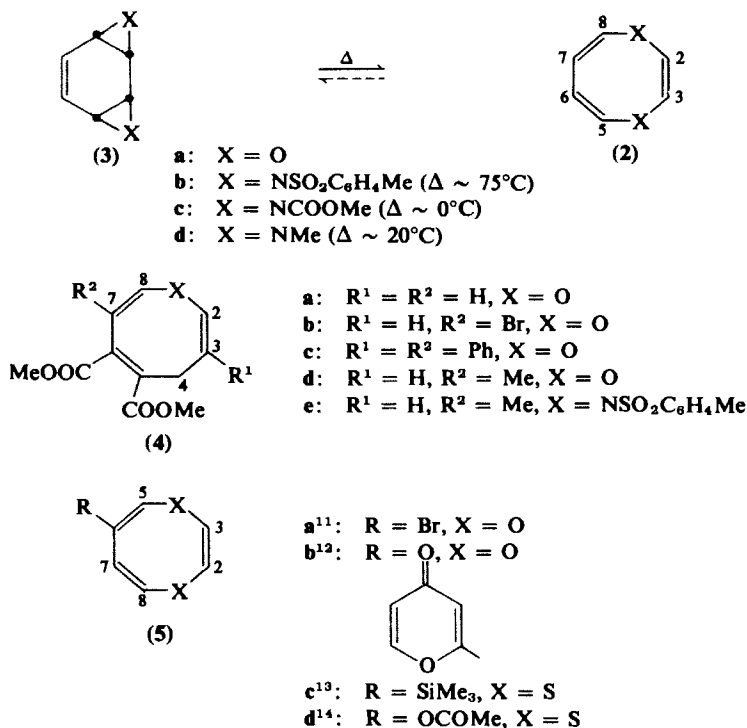
⁵ A. T. Balaban and Z. Simon, *Rev. Roum. Chim.* **10**, 1059 (1965).

⁶ B. A. Hess and L. J. Schaad, *J. Am. Chem. Soc.* **95**, 3907 (1973).

⁷ H.-J. Altenbach and E. Vogel, *Angew. Chem., Int. Ed. Engl.* **11**, 937 (1972).

⁸ H. Prinzbach, M. Brenninger, B. Gallenkamp, R. Schwesinger, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.* **14**, 348 (1975).

⁹ D. Stusche, M. Breuninger, and H. Prinzbach, *Helv. Chim. Acta* **55**, 2359 (1972).



SCHEME 1

pyrolytically from bisepisulfide 3(X = S) have been frustrated by the tendency of this substance rapidly to extrude sulfur on mild warming (20°C).¹⁰ Besides the various molecules formulated under 2 and 4, a number of 6-substituted 1,4-diheterocins, i.e., 5, have also been prepared in recent years.¹¹⁻¹³

Table I lists NMR information that proved useful in understanding the π -electronic requirements of the basic 1,4-diheterocin system. The 1,4-dioxocin molecule (2a) may thus be classed as nonaromatic,⁷ based on the close similarity of its proton shifts with those displayed by the family's monohetero polyenic models (4a and b), whereas the fact that

¹⁰ E. Vogel, E. Schmidbauer, and H.-J. Altenbach, *Angew. Chem., Int. Ed. Engl.* **13**, 736 (1974).

¹¹ E. Vogel, H.-J. Altenbach, and D. Cremer, *Angew. Chem., Int. Ed. Engl.* **11**, 935 (1972). This paper also describes the conversion of bromide (5a) to parent 1,4-dioxocin by tri-*n*-butyltin hydride.

¹² D. B. Borders and J. E. Lancaster, *J. Org. Chem.* **39**, 435 (1974).

¹³ H. J. Eggelte and F. Bickelhaupt, *Angew. Chem., Int. Ed. Engl.* **13**, 345 (1974).

TABLE I
PROTON NMR CHARACTERISTICS OF CERTAIN MONOHETERO- AND
DIHETERO[8]ANNULENES^a

Compound	Chemical shifts (τ)						Coupling constants (Hz)			
	H ² , H ³	H ⁵	H ⁶	H ⁷ , H ⁸	N-ME		J _{2,3}	J _{6,8}	J _{6,7}	J _{7,8}
2a ^b	4.00 —	3.41	4.88	— —	—	—	—	8.0	9.2	—
2b ^c	3.69 —	3.62	4.53	— —	—	—	—	—	—	—
2c ^c	3.99 —	3.77	4.38	— —	—	—	—	—	—	—
2d ^c	4.12 —	3.50	4.37	— —	6.02	—	—	—	—	—
5a ^b	4.06, 4.20	3.15	—	4.63, 3.72	—	4.2	—	—	—	7.5
5d ^c	3.81, 3.95	4.24	—	4.00, 3.08	—	9.0	—	—	—	9.0
4a ^b	3.85, 4.83	—	—	4.73, 3.89	—	6.4	—	—	—	7.4
4b ^b	3.79, 5.13	—	—	— 3.57	—	6.5	—	—	—	—
4d ^d	3.76, 5.10	—	—	— 3.99	—	6.2	—	—	—	—
4e ^a	3.42, 5.02	—	—	— 4.31	—	8.6	—	—	—	—

^a Data from Altenbach and Vogel,⁷ Prinzbach *et al.*,^{8,9} Vogel *et al.*,¹¹ and Eggelte and Bickelhaupt.¹³

^b Spectrum recorded in CCl₄.

^c Spectrum recorded in CHCl₃.

^d Spectrum recorded in CD₃CN.

(2b–d) closely resemble each other in this respect despite the significantly lower effective electronegativity of the NMe function compared to NCOOEt or NSO₂C₆H₄Me may be judged to indicate the presence of a certain degree of ring diamagnetism in the former, i.e., 2d; this latter conclusion was also arrived at from direct NMR (¹H and/or ¹³C) comparisons of 2d with the benzo analog (6b) and the corresponding triazonine, i.e., 52g (see Section II,B,2,c). The situation with the third member of the group, 1,4-dithiocin, is not as clearly defined since the molecule is not currently available in unsubstituted form. Interestingly, the proton shifts of the monosubstituted derivative (5d) were judged not to be strictly “olefinic” in nature,¹³ and it is generally agreed that there is need for more experimentation in the area.

b. *Restricted Diheterocins.* Of the two possible monobenzo-1,4-diheterocin systems, only the symmetrical modification shown in (6)^{14–16} is currently available. Benzodiazocine (6b)¹⁵ and benzodithiocin (6c)¹⁶ were synthesized pyrolytically from the corresponding [4, 2, 0]

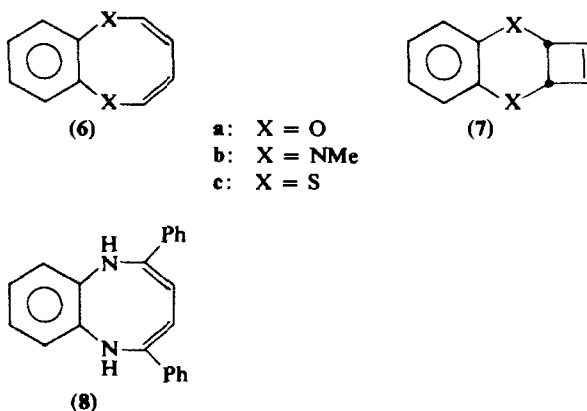
¹⁴ W. Schroth and B. Werner, *Angew. Chem., Int. Ed. Engl.* **6**, 697 (1967).

¹⁵ H.-J. Shue and F. W. Fowler, *Tetrahedron Lett.*, 2437 (1971).

¹⁶ D. L. Coffen, Y. C. Poon, and M. L. Lee, *J. Am. Chem. Soc.* **93**, 4627 (1971).

isomers (**7b** and **c**) to which they readily revert on irradiation. The third member of the group, 1,6-benzodioxocin (**6a**),¹⁴ was prepared by a sequence of condensations and eliminations, and it too undergoes photo-induced cyclization to produce **7a**. A diphenyl derivative (**8**) of *parent* benzo-1,4-diazocine was also described recently.¹⁷

With regards to classification, it is generally agreed that the proton NMR resonances displayed by the three available benzodiheterocin prototypes (**6a-c**), ranging from τ 3.05 for the protons α to oxygen in **6a** to τ 5.62 for the hydrogens β to nitrogen in **6b**, are implicative of largely localized, heavily buckled, eight-membered frames.¹⁴⁻¹⁸ On the other



hand, the two magnetically equivalent nonbenzenoid protons of the diphenyl derivative (**8**) were found to resonate at τ 3.4¹⁷ compared to τ 4.65¹⁴ and τ 5.62¹⁵ reported for their counterparts in **6a** and **6b**, respectively. It follows, that unless a major portion of this rather substantial deshielding experienced by the diazocin protons of **8** is somehow due to the proximity of the phenyl appendages, the eight-membered moiety of **8** is endowed with a certain degree of ring diamagnetism.

A few heavily annulated 1,4-diheterocin specimens are also available. They are shown in **9**,¹⁸ **10**,¹⁹ and **11**.²⁰ Compound **9** was one of the first diheterocin molecules to be synthesized and displays ¹H NMR characteristics that were judged to be inconsistent with the presence of an

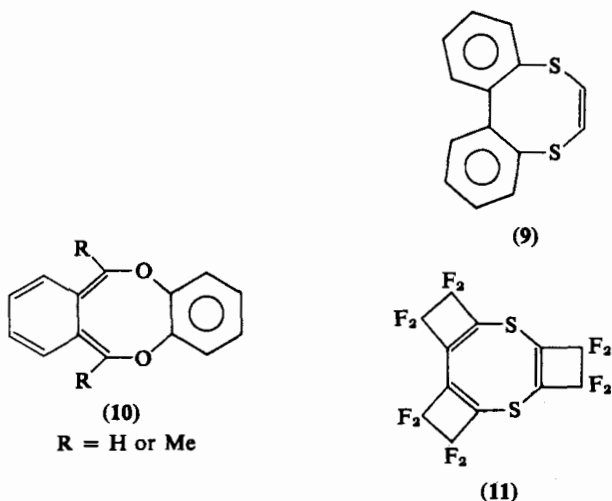
¹⁷ A. P. Bindra and E. LeGoff, *Tetrahedron Lett.*, 1523 (1974).

¹⁸ W. Schroth, F. Billig, and A. Zschunke, *Z. Chem.* **9**, 184 (1969).

¹⁹ J. Rigaudy, J. B-Lafont, M. Moreau, and N. K. Cuong, *C.R. Hebd. Seances Acad. Sci., Ser. C.* **276**, 1607 (1973).

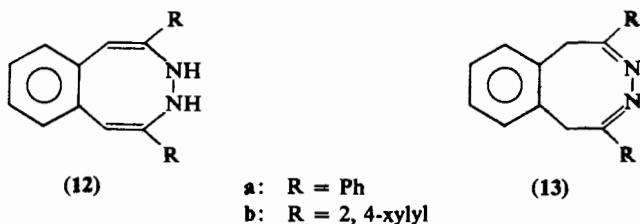
²⁰ M. O. Riley and J. D. Park, *Tetrahedron Lett.*, 2871 (1971).

aromatically delocalized eight-membered ring.¹⁸ Dioxocin (10) was thermally generated from anthracene photoperoxide and enjoys only



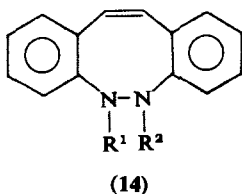
fleeting existence, rapidly isomerizing to a dibenzo variant containing a [4, 6, 0] frame.¹⁹ The triannulated dithiocin (11) is of some interest insofar as its ¹⁹F NMR shifts are claimed²⁰ to be indicative of ring diamagnetism.

Sharply contrasting the well-studied 1,4-diheterocin system, the 1,2 counterpart remains virtually unknown, its entire literature coverage being limited to two reports^{21,22} describing studies dealing with certain benzo-annulated nitrogen analogs. The first of these²¹ appears to have been prompted by the HMO prediction of rather substantial π delocalization energies for the parent system (1a; DE = 2.99 β) and its benzo derivative (12; R = H; DE = 4.76 β), which, however, could not be substantiated as the synthetic precursor shown in 13 failed to isomerize



²¹ N. L. Allinger and G. A. Youngdale, *J. Org. Chem.* **25**, 1509 (1960).

²² W. W. Paudler and A. G. Zeiler, *J. Org. Chem.* **34**, 3237 (1969).

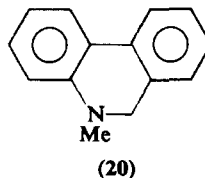
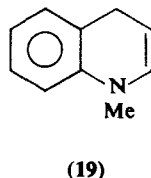
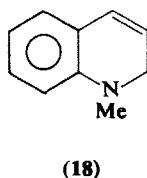
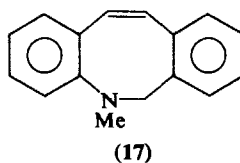
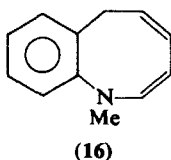
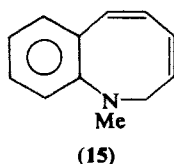


- a: $R^1 = R^2 = H$
 b: $R^1 = H, R^2 = Me$
 c: $R^1 = R^2 = Me$

to the corresponding diazocin (12) upon prolonged exposure to palladium-on-charcoal at 140°C. The second investigation²² dealt with the symmetrically diannulated derivative shown in 14, which was analyzed by UV as well as "amine-proton" NMR shifts and whose parent amine (14a) was judged on this basis to possess a system that is "at least partially planar and highly conjugated."²²

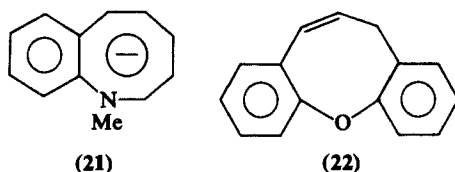
c. *Heterocinyl Anions.* Replacement of one of the heteroatomic lone pairs in a diheterocin with a homoatomic one, i.e., a carbanionic center, leads to an iso- π -electronic heterocinyl anion. Because of increased kinetic instability imparted by the presence of a negative charge, these systems are not readily amenable to direct spectroscopic examination and their classification normally draws from a comparison of C-H acidities.

Experimental work in the area has thus far been limited to a few annulated members of the family. The benzo derivatives shown in 15–17 were recently synthesized for such a study, and the base-catalyzed exchange rates of their key allylic methylene groups were determined and compared to those of models 18–20 measured under comparable conditions.²³ In each instance, the kinetic acidity of the C-H link was found



²³ R. M. Coates and E. F. Johnson, *J. Am. Chem. Soc.* 93, 4016 (1971).

to *increase* on passing from the six-membered model to the eight-membered counterparts, and, in the case of **15** and **16**, the observed acidity enhancement, 83- and 29-fold, respectively, was judged to be sufficiently pronounced to indicate some degree of "aromatic" stabilization in the incipient 10π -electron anion (**21**).²³ In other work²⁴ dealing



with measurements of *thermodynamic* acidity, dibenzoxocin (**22**) was shown to be significantly more acidic (~ 200 -fold) than its six-membered model, xanthene, thus leading to an estimated pK_a of 27 for the dibenzoxocin. It was also noted²⁴ that the experimentally determined pK_a value differs from that (24.9) calculated by Streitwieser's "formula"²⁵ correlating the pK_a of a carbon acid with the change in HMO delocalization energy attending the ionization process, the discrepancy between the two estimates being attributed to the skeletal strain developed as a result of the molecule's ability to flatten sufficiently its central ring for effective aromatic delocalization of its π electrons.

The most significant conclusion to be drawn from the results discussed in this section is that the diheterocin system is basically reluctant to realize its 10π -electron aromatic potential, although its affinity to do so gains significantly with increasing lone-pair mobility as judged by the center's effective electronegativity; compare, for example, the changes attending the passage from atropic dioxocin (**2a**) to the mildly diatropic nitrogen counterpart (**2d**) and, finally, to the strongly diatropic carbon analog, the cyclooctatetraenyl dianion (COT^{2-}). In terms of Eq. (1) the diheterocin molecule is characterized by a destabilizing $\Delta H_0^\sigma - T\Delta S_0$ combination, reflecting the effect of angle strain and flexibility, and a ΔH_0^π term consisting chiefly of an "aromatically" (10π)-stabilizing component and an electrostatically *destabilizing* contribution resulting from the distribution of the system's 10π electrons over a periphery possessing only eight nuclear centers. Within this frame of reasoning, the experimental information on the subject clearly suggests that, unlike their carbanionic relatives, heteroatomic lone pairs are not sufficiently

²⁴ H. S. Kasmai and H. W. Whitlock, *J. Org. Chem.* **37**, 2161 (1972).

²⁵ A. Streitwieser, *Tetrahedron Lett.*, 23 (1960).

mobile to generate the type of advantage needed by the stabilizing contribution of the ΔH_0^π term for the development of a well-delocalized system.

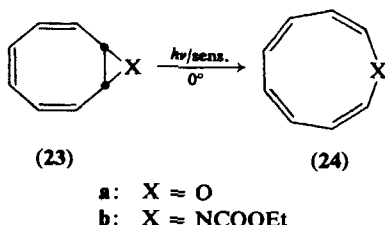
Judged on the basis of Eq. (1) the proposed diatropicity of triannulated dithiocin (**11**) may reasonably be attributed to (i) enhanced lone-pair mobility due to the presence of strongly electron-withdrawing C-annulation and (ii) reduction of skeletal adversity (ΔH_0^σ term composed largely of angle strain) resulting from the introduction of a steric component strongly favoring a planar geometry.

2. Systems with Nine π Centers

The significance of the nine-membered ring among potentially heteroaromatic molecules derives primarily from its unique size that is sufficiently large (significant $\Delta H_0^\sigma - T\Delta S_0$ component) strongly to favor a buckled geometry but not too large to prohibit the attainment of planarity should a substantial ΔH_0^π become available. In other words, what one has is a system that is capable of adjusting its shape to the demands of lone-pair delocalization, i.e., one where molecular geometry offers a direct measure of the heteroatom's affinity to merge into the π system.

a. *Parent Heteronins.*²⁶ The monohetero system depicted in **24** and commonly referred to as a heteronin is a direct heteroatomic analog of the cyclononatetraenyl anion and as such might be expected to exhibit "aromatic" character.

The parent system was prepared in the form of **24a**²⁷ and **24b**²⁸ in one photoinduced retroelectrocyclic step from its bicyclo isomer shown in **23**. In addition, a rich variety of azonines, including the acid-base pair

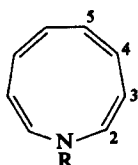


²⁶ For reviews on the subject, see (a) A. G. Anastassiou, *Acc. Chem. Res.* **5**, 281 (1972); (b) *Pure Appl. Chem.* **44**, 691 (1975).

²⁷ (a) A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 903 (1969); (b) 1521 (1969); (c) S. Masamune, S. Takada, and R. T. Seidner, *J. Am. Chem. Soc.* **91**, 7769 (1969).

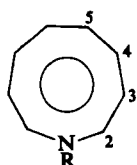
²⁸ A. G. Anastassiou and J. H. Gebrian, *J. Am. Chem. Soc.* **91**, 4011 (1969); (b) S. Masamune, K. Hojo, and S. Takada, *Chem. Commun.*, 1204 (1969).

27a^{29,30} and **b**³¹ have since become available from **24b** by base-induced exchange of its substituent. Attempts to prepare the third common member of the family, i.e., thionin (**24**; X = S) through photoinduced ring opening of episulfide **23** (X = S)³² has thus far proven unsuccessful,³³ but effort in this direction is said to be continuing.



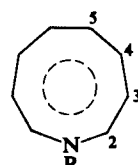
(25)

a: R = COMe
b: R = SO₂Ph
c: R = CONMe₂
d: R = CONHPh



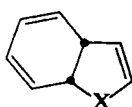
(26)

a: R = H d: R = K⁺
b: R = Li⁺ e: R = Rb⁺
c: R = Na⁺ f: R = Cs⁺

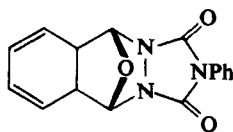


(27)

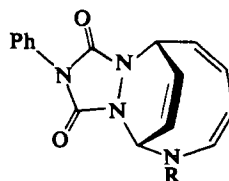
a: R = Me
b: R = Et
c: R = CH₂Ph



(28)



(29)



(30)

Heteronins **24–27** have been the subject of extensive spectroscopic and chemical studies, and it has been established that certain members, such as oxonin (**24a**) and those azonines incorporating electron-withdrawing N-substituents (**24b** and **25**) possess heavily localized polyenic frames, whereas others, such as parent azonine (**26a**) and its anion (**26b–f**), are extensively delocalized and decidedly aromatic.³⁰ A third subgroup consisting of the *N*-alkyl azonines (**27**) was said to be “non-descript”. In specific terms, the polyenic members of the family were shown to be (i) atropic by ¹H NMR, (ii) π -localized and heavily buckled by UV,³⁰ ¹³C NMR,³⁴ and an X-ray determination on urea **25c**,³⁵ (iii) thermally labile, readily isomerizing to the *cis*-bicyclo[4.3.0]triene frame

²⁹ A. G. Anastassiou and J. H. Gebrian, *Tetrahedron Lett.*, 825 (1970).

³⁰ A. G. Anastassiou, S. W. Eachus, R. P. Cellura, and J. H. Gebrian, *Chem. Commun.*, 1133 (1970).

³¹ A. G. Anastassiou and S. W. Eachus, *J. Am. Chem. Soc.* **94**, 2537 (1972).

³² A. G. Anastassiou and B. Chao, *Chem. Commun.*, 979 (1971).

³³ A. G. Anastassiou and B. Chao, *Chem. Commun.*, 277 (1972).

³⁴ A. G. Anastassiou and E. Reichmanis, *J. Am. Chem. Soc.* **98**, 8266 (1976).

³⁵ C. C. Chiang, I. C. Paul, A. G. Anastassiou, and S. W. Eachus, *J. Am. Chem. Soc.* **96**, 1636 (1974).

shown in **28** on warming to room temperature, and (iv) highly reactive toward cycloaddition, with oxonin (**24a**) yielding the (2 + 8) cycloadduct shown in **29**³⁶ and azonines (**24b**, **25a** and **c**) producing unsymmetrical (2 + 4) adducts of general structure **30**³⁷ with *N*-phenyl-triazolinedione at -78°C . By contrast, the aromatic members of the group were found to be (i) diatropic by ^1H NMR, (ii) π -delocalized and essentially planar by UV³⁰ and ^{13}C NMR,³⁴ and (iii) thermally stable; additionally 1*H*-azonine was shown to be significantly *more* (200-fold) acidic than pyrrole!³¹ Finally, the nondescript heteronins are invariably characterized by properties that are not sufficiently well developed in either direction to allow for unambiguous classification. They are, for example, endowed with only marginal thermal stability and possess spectroscopic characteristics consistent with the presence of a π system that is weakly delocalized (UV, ^{13}C NMR) and only mildly diatropic (^1H NMR); the members of this group are intermediate between the aromatic and polyenic counterparts in thermal stability as well.

The reader may gain better appreciation of the many basic differences responsible for the division into different classes of heteronin by comparing certain representative members, directly or through appropriate models, in terms of the information presented in Table II. First, one notes that the classification of oxonin (**24a**) as atropic, *N*-methylazonine (**27a**) as nondescript, and 1*H*-azonine or its anion as diatropic, originally proposed on the basis of ^1H NMR chemical shifts (data shown in first three rows), was confirmed by the determination of solvent shift character (*S* values)^{38,39} that revealed 1*H*-azonine to possess significant diatropic influence (comparable to that of naphthalene; $+1.35^{38}$), the *N*-methyl counterpart to exhibit a far weaker effect *in the same direction*, and oxonin to be atropic or mildly paratropic under this criterion, its *S* value being closely similar to that of the family's 8π -electron polyenic model, all-*cis*-cyclononatetraene (**24**; $\text{X} = \text{CH}_2$). Major differences between oxonin and parent azonine are also seen to exist in terms of thermal stability and ^{13}C NMR and UV spectroscopy, all of which serve further to emphasize the close structural similarity of oxonin with π -

³⁶ A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 484 (1970).

³⁷ A. G. Anastassiou, R. P. Cellura, J. M. Spence, and S. W. Eachus, *Chem. Commun.*, 325 (1972).

³⁸ This useful procedure, whereby solvent anisotropy is measured in terms of an *S* value defined by the ratio $\tau(\text{X}) - \tau(\text{C}_6\text{H}_{12})/60$, where $\tau(\text{X})$ is the difference in chemical shift between cyclohexane and acetonitrile in solvent X and $\tau(\text{C}_6\text{H}_{12})$ is the analogous difference in cyclohexane solvent, was developed by F. A. L. Anet and G. E. Schenck, *J. Am. Chem. Soc.* **93**, 556 (1971).

³⁹ A. G. Anastassiou and H. Yamamoto, *Chem. Commun.*, 286 (1972).

TABLE II
SPECTROSCOPIC AND THERMAL STABILITY CHARACTERISTICS OF CERTAIN HETERONINS AND RELATED MODELS^a

Property	Compound						
	CNT ^b	24a	24b	27a	26a	26d	CNT ^{-c}
Proton shifts (τ) ^d							
H ²	—	3.75	3.63	4.15	2.93	1.36	—
H ³	—	4.90	4.68	5.12	4.00	~3.37	—
H ⁴ , H ⁵	—	4.1–4.2	4.13	3.9–4.0	3.0–3.3	~3.37	—
$J_{H,H}$ (Hz) ^d							
H ² –H ³	—	7.0	9.6	10.5	11.0	—	—
Carbon-shifts (ppm)							
(C ⁴ + C ⁵)/2	128.54	127.02	—	121.75	117.61	113.28	109.5
$J_{O,H}$ (Hz) ^e							
(C ⁴ – H + C ⁵ – H)/2	157	158	—	153	152	140	137
<i>S</i> values ^f	–0.05	–0.07	—	+0.34	+1.35	—	—
Low-energy UV band (nm) ^g	248	253	265	303	335	339	320
Thermal half-life (min) ^h	10	3	14	~240	>6000	stable	stable
Controlling component in Eq. (1)	$\Delta H_0^g - T\Delta S_0$?	ΔH_0^g		

^a See Anastassiou²⁸ for reviews giving these data.

^b 1,3,5,7-Cyclononatetraene.

^c Cyclononatetraenyl anion.

^d Recorded in CDCl₃ for 24a and b and in acetone-d₆ for 27a, 26a and d.

^e Recorded in acetone-d₆ for CNT (24a and b, 27a, 26a), in DMSO-d₆ for 26d, and in THF-d₆ for CNT.

^f See footnote 38 for a description of this property.

^g Recorded in C₆H₁₄ for CNT, 24a and b, 27a, 26a and in THF for 26d, CNT⁻.

^h Measured at 50°C.

localized 1,3,5,7-cyclononatetraene (CNT), on the one hand, and 1*H*-azonine or its anion with the planar, delocalized,⁴⁰ 10 π -electron CNT anion (**24**; X = $\bar{\text{C}}\text{H}$), on the other.⁴¹ These similarities were strongly stressed in the recent description of ¹³C NMR data³⁴ that were judged to be explicitly indicative of a direct relationship between lone-pair delocalization and molecular flattening.

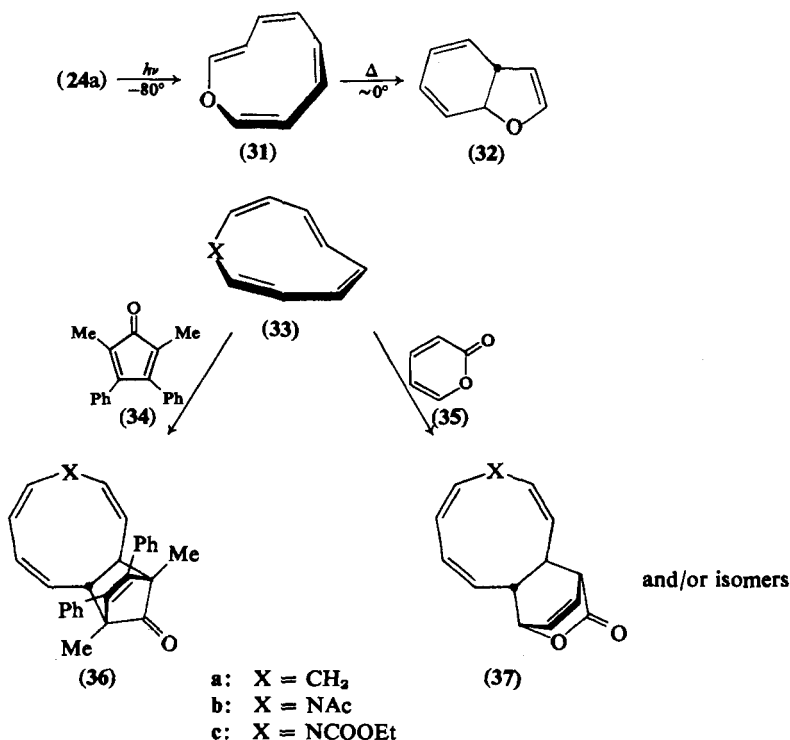
The last row of Table II lists those energy contributions of Eq. (1) which are believed to be dominant in each case, i.e., $\Delta H_0^\sigma - T\Delta S_0$ for the cyclopolyenes and ΔH_0^π for the corresponding aromatics. Since the (ΔH_0^σ , ΔS_0) contribution should, for obvious reasons, be roughly the same in *all* the readily classifiable heteronins, the inability of some members to flatten and thus generate proper environment for π delocalization, must certainly be attributed to a reduced ΔH_0^π term. Further, bearing in mind that the polyenic heteronins are invariably those associated with the more electronegative heteroatomic units, one is drawn to the inevitable conclusion that it is chiefly because of reduction in lone-pair mobility that the magnitude of the ΔH_0^π contribution in **1** (Section II,B,1,a) drops to the point where it can no longer overcome the combined adversity of skeletal flexibility and σ strain. Within this frame of reasoning the nondescript nature of *N*-alkyl azonines (**27**) whose lone-pair mobility and, hence, ΔH_0^π contribution should clearly be comparable in magnitude to that of the aromatic parent (**26a**) is best viewed to arise from proper balance of opposing σ and π effects, the added σ component responsible for the attainment of this balance being contributed by the repulsive nonbonded interaction of the *N*-alkyl appendage with the two "ortho" protons. For obvious reasons, the existence of nondescript heteronins indicates that the advantage held by ΔH_0^π in the aromatic members of the family must not be particularly large. The results of a recent variable-temperature NMR study on 1*H*-azonine (**26a**)^{28b} revealing the existence of thermally induced skeletal distortion are certainly consistent with this view.

Brief examination of "Dreiding" molecular models reveals that unrestricted heteronins incorporating one or more trans double bonds will

⁴⁰ H. E. Simmons, D. B. Chestnut, and E. A. LaLancette, *J. Am. Chem. Soc.* **87**, 982 (1965).

⁴¹ A recent Hückel calculation based on the proper choice of models correctly accounts for the observed differences in π -electronic makeup between 1*H*-azonine (**26a**) and oxonin (**24a**) which were calculated to possess resonance energies of 0.139 and 0.001 β , respectively [B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron* **28**, 3657 (1972)]. In terms of simple Hückel theory the differences between **26a** and **24a** were attributed chiefly to the lower LVMO energy of the latter (A. G. Anastassiou, in "Topics in Nonbenzenoid Aromatic Chemistry" (T. Nozoe, R. Breslow, K. Hafner, S. Ito, and I. Murata, eds.), Vol. I, pp. 1-27. Hirokawa Publ., Tokyo, 1973).

be skeletally destabilized relative to the all-cis counterparts. It is not surprising then to find that the few reports that make specific mention of such molecules do so in terms of their transient existence. In the first of these it was argued that the photothermolytic conversion of epoxide (23a) partially to the trans-fused dihydrobenzofuran (32) constitutes evidence for the fleeting intermediacy of *cis*,³ *trans*-oxonin (31)^{27c} although the possibility that the mono-*trans* monocycle might actually be the *cis*,² *trans*, *cis* position isomer of 31 was not eliminated. In other work,^{42,43} the general *cis*,² *trans*, *cis* nine-membered frame (33a, b, c) was generated on mild thermolysis (ca. 65°C) of 23 (X = CH₂, NAc, NCOOEt) and characterized through cycloadditive trapping with the cyclopentadienone (34)⁴² and α -pyrone (35)⁴³ to yield symmetry-allowed 1:1 adducts 36 and 37, respectively.



⁴² (a) A. G. Anastassiou, R. L. Elliott, H. Wright, and J. Clardy, *J. Org. Chem.* **38**, 1959 (1973); (b) A. G. Anastassiou and R. C. Griffith, *J. Am. Chem. Soc.* **93**, 3083 (1971).

⁴³ (a) A. G. Anastassiou, E. Reichmanis, and R. L. Elliott, *Tetrahedron Lett.*, 3805 (1973); (b) A. G. Anastassiou, S. S. Libsch, and R. C. Griffith, *Tetrahedron Lett.*, 3103 (1973).

b. *Restricted Heteronins*. A variety of structurally confined heteronins were prepared and studied in recent years.

The simple benzoannulated derivatives (**38b** and **c**) and the hydrocarbon model (**38a**) were synthesized from cycloadducts **37** by a two-step sequence entailing thermal extrusion of CO₂ followed by juncture dehydrogenation with *o*-chloranil.⁴³

In line with earlier findings discussed in the preceding subsection, benzazonines (**38b** and **c**) were shown to possess polyenic nine-membered segments closely resembling the hydrocarbon model (**38a**) by NMR and UV.⁴³ The parent amine (**39**)⁴⁴ (prepared from **38b**) and the corresponding amide (**40**)⁴⁴ also were found, perhaps unexpectedly, to incorporate heavily localized heteronin moieties. The similarity among N-substituted benzazonines (**38b** and **c**), benzocyclononatetraene (**38a**), and parent benzazonines (**39** and **40**) may safely be deduced from the pertinent spectroscopic information listed in Table III.

TABLE III
SPECTROSCOPIC CHARACTERISTICS OF CERTAIN MONOBENZOHETERONINS^a

Property	Compound					
	38a	38c	42	39	40	41
Proton shifts (τ) ^b						
H ^a		5.32	4.97	5.71	6.23	4.35
H ^b		4.27	3.22	4.37	3.72	2.24
$J_{\text{H},\text{H}}$ (Hz) ^b						
H ^a -H ^b		10.0	10.5	10.0	8.5	6.5
H ^a -H ^c		5.5	7.5	< 2	4.5	10.0
Low-energy						
UV band (nm) ^c	240	267	345	290		

^a Data from Ref. 26b.

^b Recorded in benzene-d₆ for **38b**, in acetone-d₆ for **39**, **42**, and in liquid ammonia for **40**, **41**.

^c Recorded in C₆H₁₄.

Benzoannulation is thus seen to inhibit lone-pair delocalization in 1*H*-azonine and its anion. The key operational question, of course, is, does this happen because of a reduction in the molecule's ΔH_0^n contribution to Eq. (1) or does it result from an increase in the σ strain (ΔH_0^σ term) possibly because of the development of skeletal restrictions not

⁴⁴ A. G. Anastassiou and E. Reichmanis, *Angew. Chem., Int. Ed. Engl.* **13**, 404 (1974).

present in the unconstrained system? The answer to this question was given by a single crucial observation,⁴⁵ namely that benzopolyenic amide (**40**) readily undergoes cis-trans isomerization to (**41**) on warming to 0°C and, most important, that this largely unexpected transformation occurs with the development of aromatic character, the pertinent ¹H NMR information in Table III attesting to the molecule's diatropicity. Operationally, this observation was interpreted to mean that benzoannulation adversely affects the development of delocalization in the nine-membered segment of **40** not because of any major π -electronic perturbation but rather because it generates two sets of peripheral (peri) H-H interactions about the ring juncture that prevent the azonine moiety from attaining the planarity necessary to properly mobilize the lone pair into delocalization. Specifically, it was pointed out^{45,46} that isomerization of **40** to **41** serves to eliminate entirely one "peri" interaction and possibly alleviate the other, thus allowing the originally buckled azonine segment to undergo the type of flattening required for the development of a π -delocalized periphery. Further, (i) parent azoninyl anion (**26b**) shows no tendency to thermally isomerize to a trans form and (ii) the carbocyclic analog, i.e., the cyclononatetraenyl anion, actually undergoes the reverse transformation, i.e., trans \rightarrow cis, on warming.⁴⁷ Hence it is concluded that there are serious peri interactions in **40** that make a large contribution to the molecule's ΔH_0^σ term, sufficient to overcome the rather substantial ΔH_0^π associated with **26**.

It is interesting to note that the same type of peri interaction was shown⁴⁸ to plague the cis⁴-benzocyclononatetraenyl anion, the iso- π -electronic carbocyclic analog of **40**, but here the resulting ΔH_0^σ term (very likely comparable to that of **40**) is not sufficiently large to overcome the larger ΔH_0^π term resulting from the greater mobility of the homoatomic lone pair and the nine-membered segment of the molecule retains its aromatic character. The severity of the skeletal restriction introduced by the H-H effect in this carbanion was, nonetheless, clearly demonstrated⁴⁹ by its affinity to undergo the same type of cis \rightarrow trans isomerization as was described for **40** although at a slower pace ($\Delta\Delta G^\ddagger = 6$ kcal/mole) since now aromaticity is not acquired but merely retained.

The pyridazinoheteronins shown in **43a-d**^{50,51} of which **43d** represents

⁴⁵ A. G. Anastassiou and E. Reichmanis, *Chem. Commun.*, 149 (1975).

⁴⁶ A. G. Anastassiou, *Acc. Chem. Res.* **9**, 453 (1976).

⁴⁷ G. Boche, D. Martens, and W. Danzer, *Angew. Chem., Int. Ed. Engl.* **8**, 984 (1969); G. Boche, and A. Bieberbach, *Tetrahedron Lett.*, 1021 (1976).

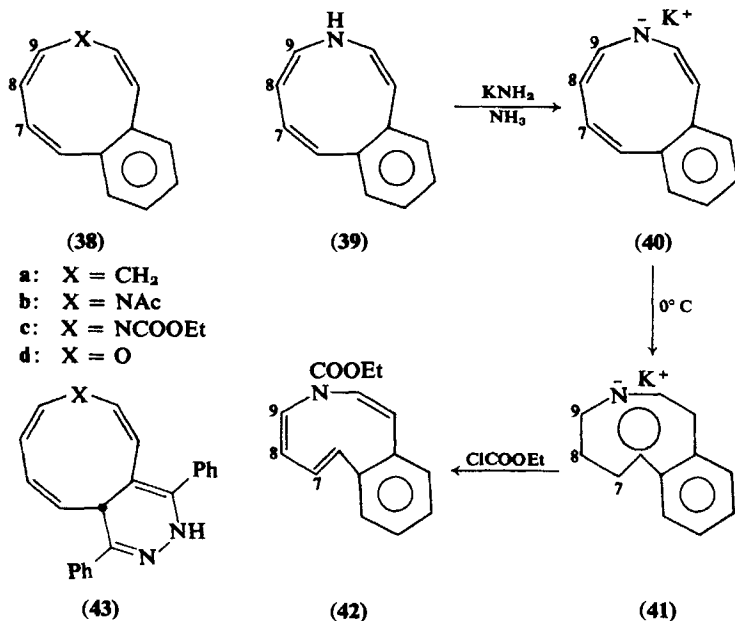
⁴⁸ A. G. Anastassiou and R. C. Griffith, *J. Am. Chem. Soc.* **96**, 611 (1974).

⁴⁹ A. G. Anastassiou and E. Reichmanis, *Angew. Chem., Int. Ed. Engl.* **13**, 728 (1974).

⁵⁰ A. G. Anastassiou and E. Reichmanis, *Chem. Commun.*, 313 (1976).

⁵¹ A. G. Anastassiou and S. J. Girgenti, *Angew. Chem., Int. Ed. Engl.* **14**, 814 (1975).

the only known example of a monoannulated oxonin, were recently synthesized by a sequence entailing *direct* cycloaddition of *sym*-diphenyltetrazine onto **23** followed by oxidative aromatization (*o*-chloranil) of the resulting adduct. Not surprisingly, they are all polyenic in character, closely resembling **38a** by UV and ^1H NMR.

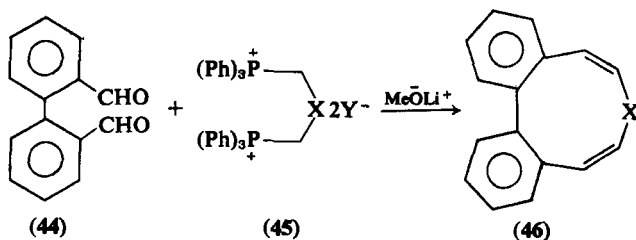


Historically, the symmetrically diannulated derivatives shown in **46a** and **b** were the first heteronin to become available.⁵² It was prepared by the condensation of dialdehyde (**44**) with difunctional Wittig reagents (**45a** and **b**) and was shown to be strictly atropic by ^1H NMR and heavily buckled by UV. Related bifunctional condensation between dialdehyde **47** and **48** gave the heavily restricted thionins **49** and **50**⁵³ which were also shown to be polyenic in nature, each resembling the corresponding sulfoxide by ^1H NMR.

In light of current information on the parent oxonin and the benzo-heteronins (**38**), it is hardly surprising to find that the highly restricted oxonin (**46a**) has polyenic character. The unavailability of appropriate

⁵² A. P. Bindra, J. A. Elix, P. J. Garratt, and R. H. Mitchell, *J. Am. Chem. Soc.* **90**, 7372 (1968).

⁵³ P. J. Garratt, A. B. Holmes, F. Sondheimer, and K. P. C. Vollhardt, *J. Am. Chem. Soc.* **92**, 4492 (1970).

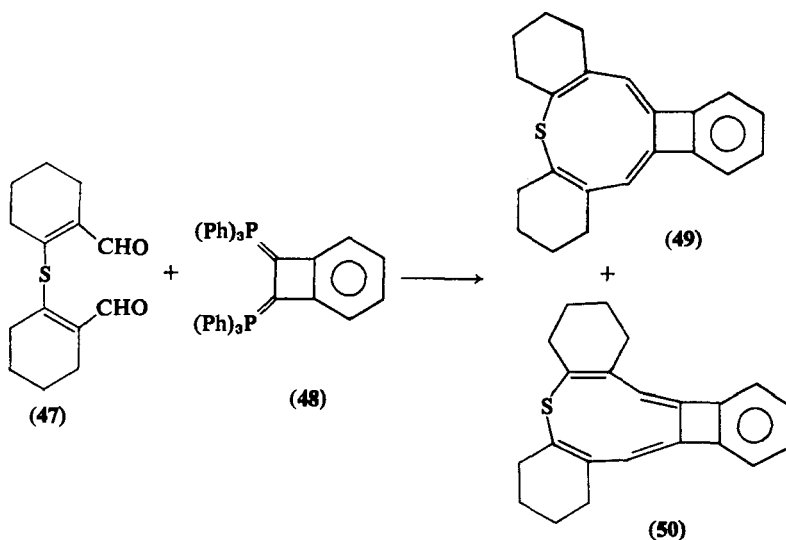


a: X = O, Y = Br

b: X = S, Y = Cl

a: X = O

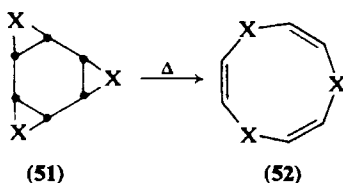
b: X = S



models, such as parent thionin and proper thia analogs of **38**, makes the situation for **46b** less straightforward. It is not, for example, entirely clear whether the lack of aromatic character in this restricted thionin is due primarily to an inadequately small ΔH_0^π term, as is believed to be the case with **46a**, or whether it is the added destabilization due to peripheral H-H interaction that tips the scales in favor of ΔH_0^σ , i.e., a situation similar to that encountered with **39**. The relatively low effective electronegativity of sulfur would appear to argue in favor of the "steric" explanation. At first glance the relative absence of peripheral H-H perturbation in **49** and, in particular, **50** might tempt one to ascribe the failure of these molecules to sustain a delocalized frame to an insufficiently mobile lone pair. Closer examination of the situation, however, reveals that this may not necessarily be the case. Specifically, one notes that the nine-membered frames of **49** and **50** are so restricted

by annulation as to be incapable of developing a delocalized frame without burdening the molecule with the destabilizing presence of a benzocyclobutadiene moiety. This electronically adverse (destabilizing contribution to ΔH_0^π) structural restriction may well be the chief factor inhibiting the development of heteronin delocalization in **49** and **50**.⁵⁴

c. *Triheteronins*. Trioxonin (**52a**)^{55,56} and triazonines (**52b–g**)⁵⁷ were recently synthesized from the all-cis tetracyclic analogs (**51**) by thermally induced $3\sigma \rightarrow 3\pi$ retroelectrocyclization, the triepoxide (**51a**) requiring significantly higher temperatures than the corresponding triaziridines. All the triheteronins listed under **52** were found to be strictly atropic by ^1H NMR. In fact, the ^1H NMR and ^{13}C NMR characteristics of **52e** were cited⁵⁷ in evidence of a highly mobile (significantly more so than the hydrocarbon model, trishomobenzene) crown conformation. The absence of π delocalization in the triheteronins is certainly not surprising. In fact, the system typifies a situation among π -excessive heteromonocycles where all the terms of Eq. (1) are destabilizing, the adverse influence of ΔH_0^π arising from the molecule's 12π ($4n$) count and also from severe electron repulsion resulting from the association of the 12π -electrons with only nine atomic centers.



- a: X = O
- b: X = NSO₂Me
- c: X = NSO₂C₈H₄Me
- d: X = NCOOMe
- e: X = NMe
- f: X = NSO₂CF₃
- g: X = NCOPh

⁵⁴ According to a recent Hückel calculation based on properly chosen models, thionin (**24**; X = S) should be endowed with a well-delocalized ($RE = 0.118\beta$) periphery (see Hess and Schaad⁶).

⁵⁵ E. Vogel, H.-J. Altenbach, and C.-D. Sommerfelt, *Angew. Chem., Chem. Int. Ed.* **11**, 939 (1972).

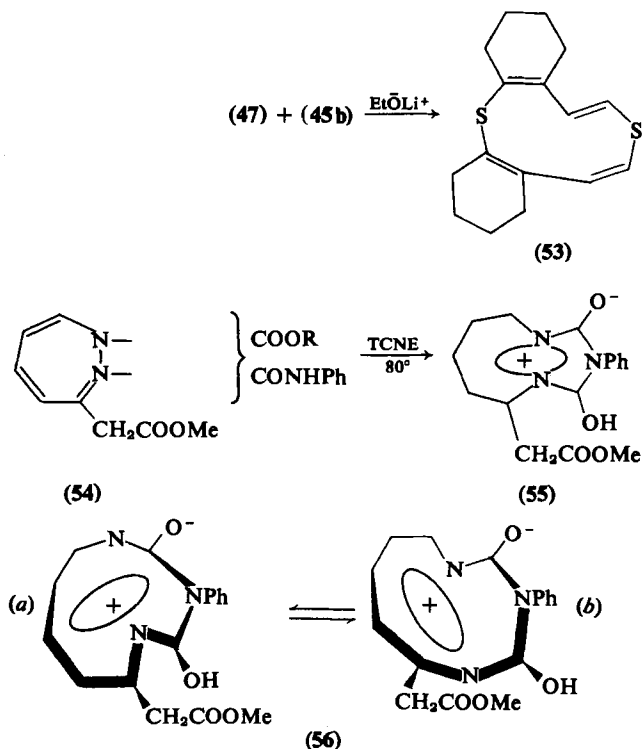
⁵⁶ R. Schwesinger and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.* **11**, 942 (1972).

⁵⁷ H. Prinzbach, R. Schwesinger, M. Breuninger, B. Gallenkamp, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.* **14**, 347 (1975).

3. Systems with Ten π Centers

This family is not a particularly populous one. At present, it appears to consist of just two fundamentally different members. The first of these, the bis-annulated 12π disulfide (**53**), was prepared by ring-forming condensation of dialdehyde (**47**) with bis Wittig reagent (**45b**).⁵⁸ It is a colorless substance characterized by unexceptional ^1H NMR absorptions. For obvious reasons, the heavily buckled atropic nature of **53** may readily be rationalized in terms of the exact same factors advanced to explain the behavior of the triheteronins.

The second member of this family is a rather unusual one. It was formed when the heavily branched diazepine (**54**) was exposed to tetracyanoethylene (TCNE) in boiling benzene and was assigned the structure depicted in **55**⁵⁹ on the basis of its UV-visible and ^1H NMR characteristics that demand that the molecule incorporate an extensively



⁵⁸ P. J. Garratt, A. B. Holmes, F. Sondheimer, and K. P. C. Vollhardt, *Chem. Commun.*, 947 (1971).

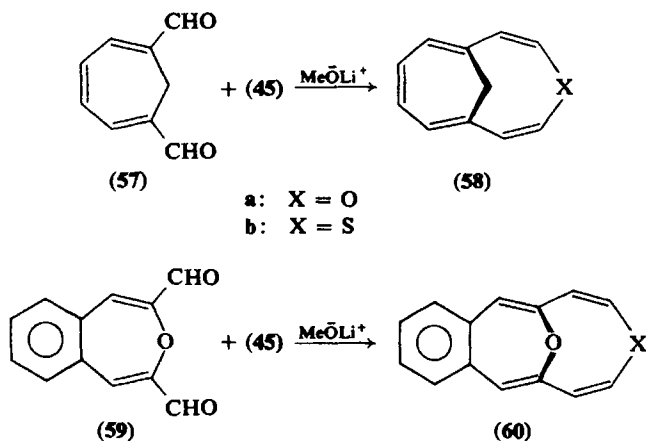
⁵⁹ T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc. C*, 2142 (1971).

delocalized strongly diatropic perimeter. Although the presence of a dominant ΔH_0^π term in this molecule obviously results from the development of a 10π -electron periphery, it is somewhat surprising that the repulsive proximity of the two "inner" nitrogen lone pairs does not prevent the molecule from assuming the necessary planar geometry. One wonders, therefore, whether the mono-trans-configurational variant, consisting of the two rapidly interconverting *planar* forms shown in **56a** and **b**, might not better describe this substance.

4. Systems with Eleven π Centers

This group has, thus far, received slightly better literature representation than the corresponding ten-atom periphery, although here too the system has yet to be synthesized in unrestricted form.

Condensation between the Wittig reagent (45) and the properly designed dialdehydes (57 and 59) has led to the general frames shown in **58**⁶⁰ and **60**⁶¹, respectively.



The ^1H NMR and UV characteristics of **58a** and **b** were shown to be consistent with a heavily buckled atropic frame and one whose heteroatomic unit is directed syn to the methano bridge.⁶⁰ It is also interesting to note in this connection that, whereas thia-annulene (**58b**) does differ rather significantly in some aspects of its NMR and UV spectra from

⁶⁰ E. Vogel, R. Feldman, H. Duwel, H.-D. Cremer, and H. Gunther, *Angew. Chem., Int. Ed. Engl.* **11**, 217 (1972).

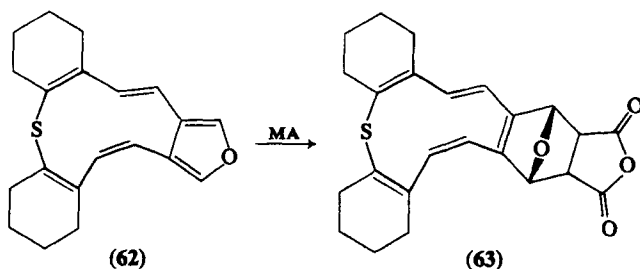
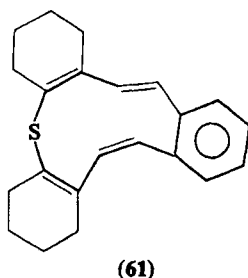
⁶¹ H. Ogawa and N. Shimojo, *Tetrahedron Lett.*, 4129 (1972).

the oxa analog (**58a**) and the corresponding hydrocarbon model, i.e., **58** ($X = CH_2$), the observed variations were attributed primarily to local diamagnetic anisotropy (NMR) and lone-pair mobility (UV) contributions of sulfur.⁶⁰

Similar observations were made with the doubly "restricted" variants **60a** and **b**.⁶¹ Here too, however, as in the case of **58**, comparison in terms of UV revealed a basic dissimilarity, with **60a** resembling the carbocyclic analog (**60**; $X = CH_2$) and **60b** displaying strong similarity to the corresponding ketone (**60**; $X = CO$).

In terms of Eq. (1), the inability of the " $4n$ "- π bridged heteroannulenes (**58** and **60**) properly to mobilize their lone pairs in delocalization obviously means that the bridging process fails to impart the type of skeletal rigidity that is necessary for ΔS_0 to overcome the combined destabilizing influence of antiaromaticity (ΔH_0^π) and skeletal strain (ΔH_0^σ).

The heavily annulated benzo- and furanothia[11]annulenes depicted in **61**⁶² and **62**⁶³ were synthesized by condensation of dialdehyde (**47**) with properly structured Wittig components. Further, treatment of **62** with maleic anhydride produced a mixture of endo and exo cycloadducts of general formula **63** whose hexatriene segment that was not directly bound to the heteroatom was found to be thermally labile, readily



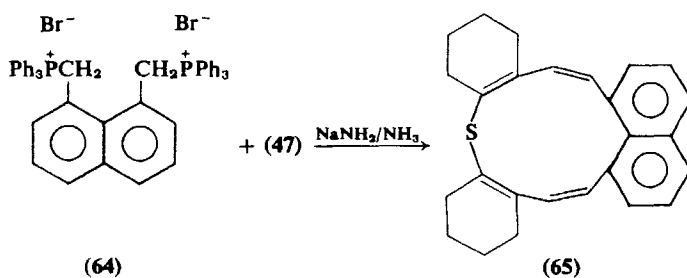
⁶² A. B. Holmes and F. Sondheimer, *J. Am. Chem. Soc.* **92**, 5284 (1970).

⁶³ A. B. Holmes and F. Sondheimer, *Chem. Commun.*, 1434 (1971).

undergoing symmetry-controlled ring closure to a trans-fused cyclohexadiene on warming to room temperature.⁶³ Compounds **61**, **62**, and **63** were shown to be atropic by NMR and are believed to possess buckled frames.^{62,63} Obviously, the restriction imposed by annulation in each case does not sufficiently deprive the central eleven-membered portion of the molecule of its ability to undergo the type of out-of-plane distortion that is necessary to prevent the development of "antiaromatic" delocalization.

5. Systems with Twelve π Centers

It appears that the only known representative of this family is the heavily annulated substance depicted in **65**, which was synthesized as shown.⁶² Being an even-membered ring and incorporating but a single π -excessive heteroatom in its periphery, the twelve-membered monocyclic moiety of **65** is somewhat unorthodox in the sense that it contains an odd number of electrons, thirteen to be exact. As a result, the central π ribbon of **65** cannot sustain delocalization without experiencing the ill effects of a π -electronic open shell. It is hardly surprising, therefore, to find that **65** exhibits UV and ¹H NMR characteristics that are indicative of a nonplanar, strictly atropic, central frame.



It is noteworthy that the development of a π -electronic open shell predicted for peripherally delocalized **65** may, in principle, be prevented through simple electron transfer to or from the remote π centers of the system's peri-fused naphthalene "tail." Derivatives of **65** with strongly electron-withdrawing, e.g., CN, NO₂, or electron-releasing, e.g., OMe, NH₂, substituents attached to the para position(s) of the naphthalene appendage would certainly be of interest.

C. LARGE FRAMES; SYSTEMS CONTAINING THIRTEEN π CENTERS AND MORE

1. *Systems with Thirteen π Centers*

This group of compounds has received ample literature representation in recent years, the basic system being known in unrestricted as well as variously constrained forms.

a. *Parent Hetero[13]annulenes.*⁶⁴ A variety of configurationally isomeric, "unrestrained," aza-⁶⁵⁻⁶⁹ and oxa[13]annulenes⁷⁰ were prepared through direct or sensitized photoinduced retroelectrocyclization as shown in the first part of Scheme 2. All configurational and specific rotameric assignments indicated in this scheme were made on the basis of ¹H NMR data. In the case of **68** and **74** the spectroscopic information was not sufficiently explicit to warrant structural commitment, but there appears to be no serious question concerning the monocyclic nature of these substances.^{64a} The various photosynthesized monocycles, including those whose structures remain unspecified, were shown to be strictly atropic by ¹H NMR and are believed to be nonplanar. Judging from earlier observations regarding the development of "aromaticity" in the heteronin family (see Section II,B,2,a), the preference shown by **68**, **69**, **71**, **74**, and **75** (or **76**) for π localization may reasonably be attributed to the low mobility of the lone pairs associated with O, NCOOEt, and NCOMe. Fully in accord with this view, one finds amines (**78**, **80a** and **b**) and amides (**77** and **81**) to possess well-delocalized diatropic frames.

The NMR information listed in Table IV offers rather striking demonstration of the decisive effect that heteroatom electronegativity has on the development of "aromaticity": the "inner" α -proton resonance of the general system depicted in **79** experiences an upfield shift in excess of 8 ppm on passing from atropic **71** to diatropic **81**! A particularly interesting observation concerning the importance of frame effects in the

⁶⁴ For reviews on the subject see (a) G. Schröder, *Pure Appl. Chem.* **44**, 925 (1975); (b) Anastassiou^{26b}; (c) Anastassiou.⁴⁶

⁶⁵ G. Schröder, G. Frank, and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.* **12**, 328 (1973).

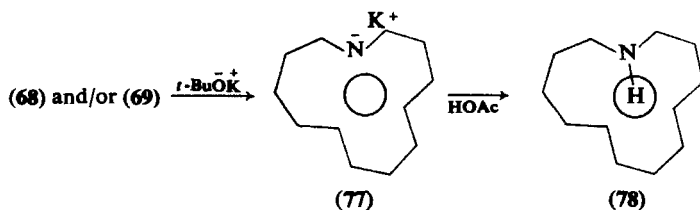
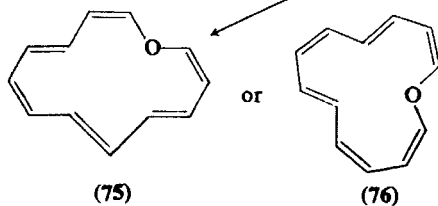
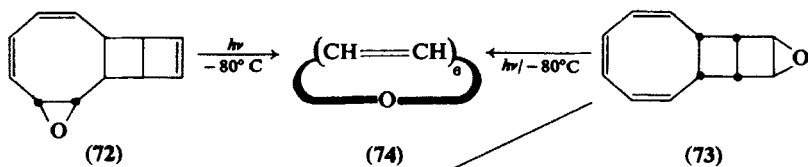
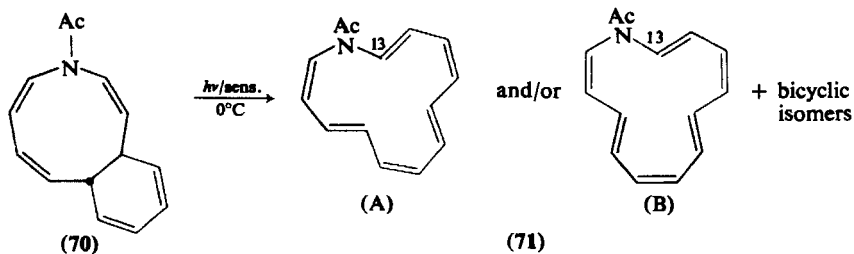
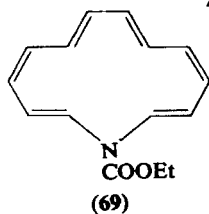
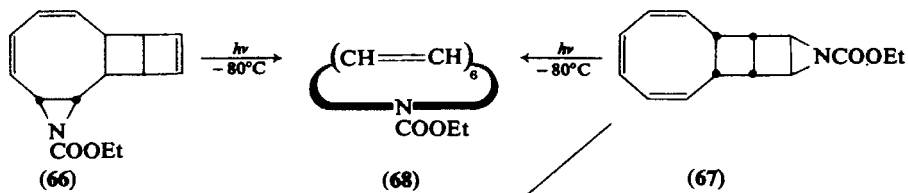
⁶⁶ G. Schröder, G. Frank, H. Röttele, and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.* **13**, 205 (1974).

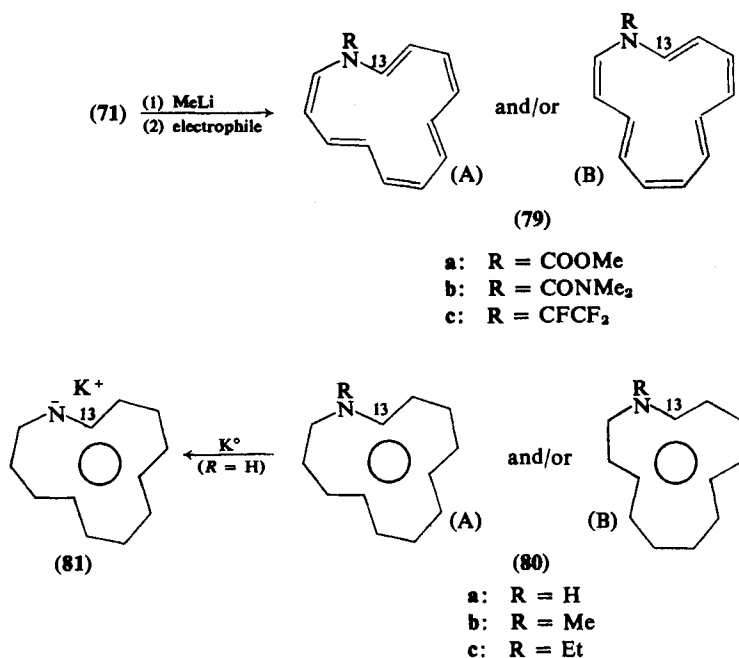
⁶⁷ A. G. Anastassiou and R. L. Elliott, *J. Am. Chem. Soc.* **96**, 5257 (1974).

⁶⁸ A. G. Anastassiou, R. L. Elliott, and E. Reichmanis, *J. Am. Chem. Soc.* **96**, 7823 (1974).

⁶⁹ G. Frank and G. Schröder, *Chem. Ber.* **108**, 3736 (1975).

⁷⁰ W. Henne, G. Plinke, and G. Schröder, *Chem. Ber.* **108**, 3753 (1975).





SCHEME 2

TABLE IV
SPECTROSCOPIC CHARACTERISTICS OF CERTAIN UNRESTRICTED AZA[13]ANNULENES^a

Compound	NMR constants ^b of inner α -hydrogen (H^{13})		UV spectra (nm) ^c	
	Chemical shift (τ)	Coupling constant (Hz)	Weak band	Strong band
71	<4.2	—	350	260
79a	<4.2	—	335	263
79b	4.50	14.0	350	280
79c	5.30	14.5	334	278
80a	7.22	14.5	360	297
80b	7.37	14.0	360	300
81	12.5	14		

^a Data from Anastassiou and co-workers.^{97,98}^b Recorded in CDCl₃ (+35°C) for 71, 79a and b, in acetone-d₆ (~0°C) for 79c, 80a and b, and in THF-d₈ (-60°C) for 81.^c Recorded in C₆H₁₄.

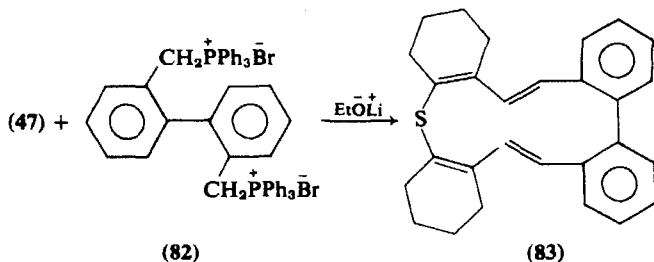
aromatically stabilized aza[13]annulenes is the ready configurational isomerization of **81** to **77** whose driving force was attributed to the release of inner-proton strain attending the transformation (three inner-protons in **81** as opposed to only two in **77**).⁶⁸ In keeping with this explanation, the configurationally isomeric amines (**78** and **80a**), both of which contain *three* centrally directed protons, were found not to interconvert on heating.⁶⁷

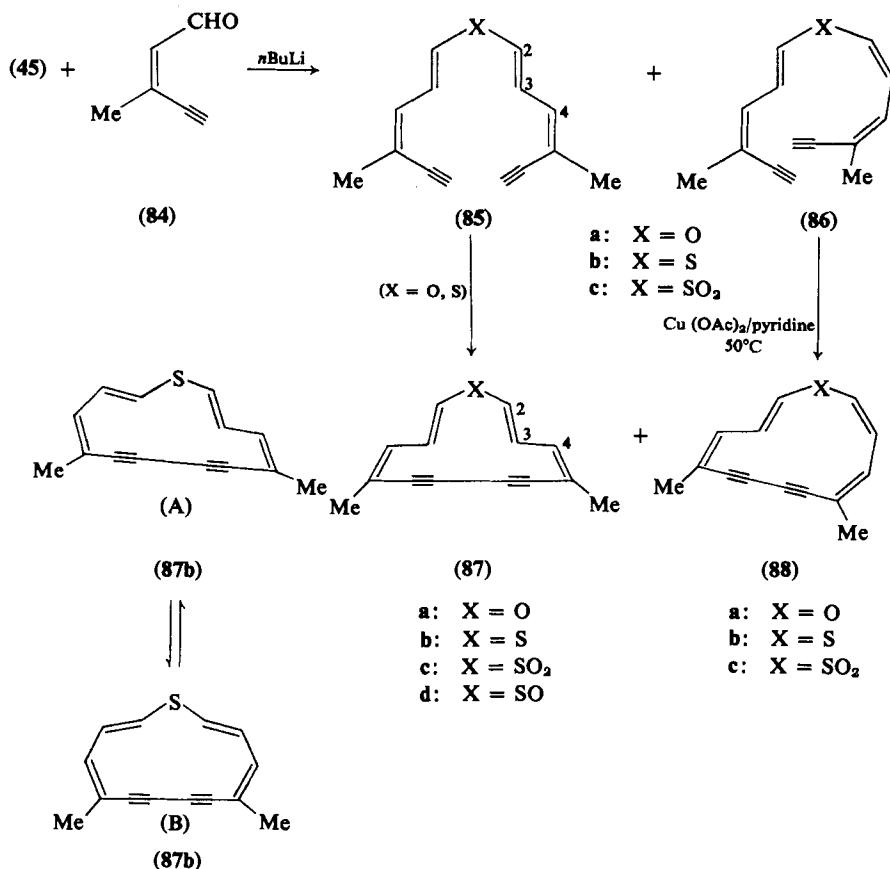
Judged in terms of Eq. (1) the conversion of **81** to **77** is believed to occur because of two related changes (i) a significant decrease in ΔH_0^σ due to reduced inner-hydrogen strain and (ii) an increase in ΔH_0^π due to enhanced planarity.

b. *Restricted Hetero*[13]annulenes. "Restricted" members of the series are known both in annulated and dehydro form.

The heavily annulated species depicted in **83** was prepared through ring-forming condensation between the bifunctional Wittig reagent (**82**) and the synthetically versatile dialdehyde (**47**).⁶² The molecule does not sustain a ring current and is believed to be nonplanar as required by the presence of a dominant ΔH_0^σ term in Eq. (1) and one which probably operates under the combined influence of peripheral and central H-H repulsion.

The geometrically isomeric bisdehydroannulene frames (**87** and **88**) and their respective acyclic models (**85** and **86**) were cleverly constructed by the sequence of condensations shown in Scheme 3. Direct comparison by ¹H NMR of the di-trans isomer (**87**) with its acyclic counterpart (**85**) and also with properly designed homocyclic models, i.e., **87** (X = CO, CHOH), has led to the classification of sulfide (**87b**) as diatropic. Specifically, one notes from the information listed in Table V that changing the molecular environment from **85b** to **87b** leads to a significant upfield shift of the resonance due to inner proton H³ and an equally meaningful downfield shift of the signals assigned to "outer" proton H⁴ and those associated with the molecule's methyl appendage. It is interesting to note that the seemingly inconsistent *upfield* shift observed in the





SCHEME 3

case of outer proton H^2 of **87b** was attributed to the possible presence of rotameric variants such as **87b(A)** and **87b(B)** where one or both of the molecule's α protons are now associated with an "in-cavity" environment.⁷¹ Comparison of the corresponding sulfone along similar lines revealed the molecule to be atropic, the differences in chemical shift observed on passing from **85c** to **87c** closely resembling those displayed by the corresponding homocyclic alcohols **85** and **87** (X = CHOH). Related comparisons in the case of oxa-annulene (**87a**), whose chemical shifts are intermediate between those displayed by **87b** and **87c**, justify the classification of this molecule as "weakly diatropic."⁷¹

⁷¹ R. L. Wife and F. Sondheimer, *J. Am. Chem. Soc.* **97**, 640 (1975).

TABLE V
PROTON NMR SHIFTS OF CERTAIN RESTRICTED HETERO[13]ANNULENES
AND RELATED MODELS^a

Compound	Proton shift ^b (τ)			
	H ²	H ³	H ⁴	Methyl
87a	3.87	5.09	3.14	7.90
87b	4.49	5.40	2.80	7.71
87c	5.05	2.90	3.07	7.87
87d	5.28	3.32	3.10	7.90
87 (X = CHOH)	5.52	3.90	3.32	8.01
87 (X = CO)	3.92	0.64	3.74	8.29
Δ (87-85)				
X = O	+0.56	+1.35	-0.60	-0.15
X = S	+0.85	$\sim +1.8$	-0.93	-0.37
X = SO ₂	+1.35	+0.52	-0.56	-0.08
X = CHOH	+1.26	+0.61	-0.41	-0.06
X = CO	+0.35	-1.71	+0.17	+0.28

^a Data from Wile and Sondheimer.⁷¹

^b All determinations were made in CDCl₃.

In contrast to **87b**, the geometric isomer in **88** was shown to resist the development of π delocalization irrespective of the nature of X, the substances listed under **88** having been found to be uniformly unstable and strictly atropic by ¹H NMR.

The loss of aromatic character suffered by the thirteen-membered sulfide on passing from the di-trans arrangement of **87b** to the mono-trans of **88b** obviously results from the inability of the latter to adopt a planar geometry and may best be described as a situation where ΔH_0^σ becomes dominant in Eq. (1) because of a large "angle-strain" component.

When judged in its entirety, the information currently available on the hetero[13]annulenes allows one to draw the following conclusions: (i) the presence of a highly mobile lone pair such as those associated with N⁻, NH, and S may induce the system to undergo the type of skeletal flattening that is necessary for π delocalization only when two or three trans double bonds are present, e.g., **77**, **78**, **87b** and **80**, **81**, respectively but not when one such function is available, cf. **88b**; and (ii) the skeletal restriction imposed by the presence by two properly located acetylenic units imparts sufficient rigidity (ΔS_0 advantage) to the system to allow

for detectable mobilization of lone pairs which are normally localized when associated with "unrestricted" frames [compare, for example, **87a** with **74** and **75** (or **76**)].

2. Systems with Fourteen π Centers

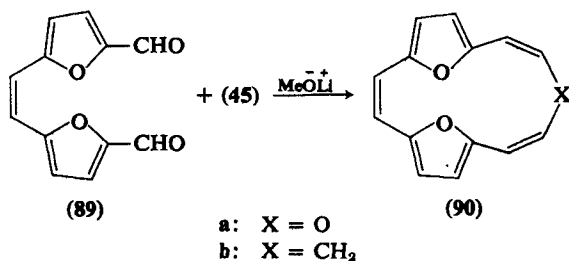
No representatives of this system appear to be available at present.

3. Systems with Fifteen π Centers

This potentially antiaromatic (16π) family has yet to be known in parent form, although certain interesting "restricted" members are available.

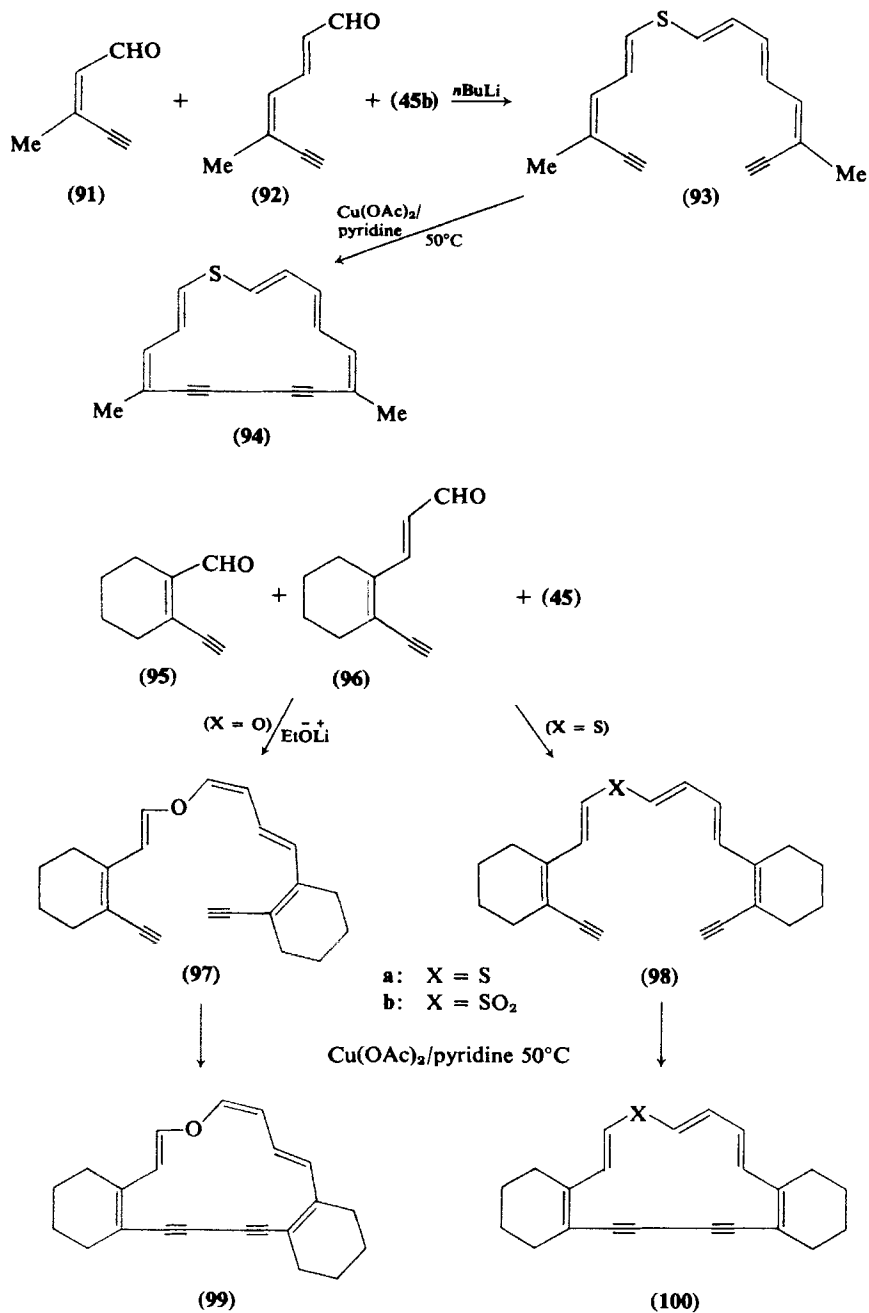
The twice oxygen-bridged systems shown in **90** were prepared⁷² from the dialdehyde (**89**) and the Wittig reagents (**45**; $X = O, CH_2$). The fifteen-membered oxide (**90a**) was recognized as the first example of a paratropic heteroannulene, its 1H NMR resonance manifold experiencing an upfield shift of 0.8 to 1.2 ppm (a value of meaningful magnitude for outer protons), relative to that of homocyclic prototype (**90b**).⁷² Interestingly, all attempts to synthesize the corresponding sulfide (**90**; $X = S$) by the same general condensation procedure were reported to have been unsuccessful, the failure to isolate the desired thia-annulene being attributed to overall instability stemming from increased antiaromaticity (compared to **90a**) because of enhanced lone-pair mobility.

Bisdehydrothia-annulene (**94**) and the annulated bisdehydrooxa- and thia-annulenes (**99** and **100**) were synthesized⁷³ in two steps as shown in Scheme 4, the key initial step entailing cross-condensation of **45** with properly designed dialdehydes. Acyclic models (**93**, **97**, and **98**) were reported to be quite unstable, and this appears to have prevented their



⁷² H. Ogawa and M. Kubo, *Tetrahedron* **29**, 809 (1973).

⁷³ R. L. Wife, P. J. Beeby, and F. Sondheimer, *J. Am. Chem. Soc.* **97**, 641 (1975).



SCHEME 4

use for purposes of direct comparison with the corresponding annulenes. Nonetheless, comparison between sulfides **94** and **100** and the reportedly atropic sulfoxide analogs by ^1H NMR has served to characterize the two thia-annulenes as paratropic. On the other hand, the ^1H NMR spectrum of oxa-annulene (**99**) was judged to be indicative of largely atropic character. The absence of antiaromatic delocalization in **99** was attributed chiefly to the molecule's skeletal inability to assume a sufficiently flat shape, possibly because of its association with only two trans double bonds as compared to three such units in **94** and **100**.

The information described in this section allows one to formulate certain generalizations regarding the development of " $4n$ "- π delocalization among hetero[15]annulenes. First, it must be realized that since the molecule is not expected to derive energetic benefit from such "antiaromatic" mobilization, its development must somehow be imposed onto the system. For obvious reasons, this is best accomplished by forcing the molecule to adopt a rigidly planar or nearly planar geometry so that only when properly "restricted" would a member of this family be expected to sustain a π -delocalized periphery. Within this frame of reasoning, sulfides **94** and **100** appear to be sufficiently well constrained for antiaromatic mobilization of their loosely held sulfur lone pairs, and the twice-bridged relative depicted in **90a** seems to be equally well disposed in this respect for effective delocalization of its more tightly held oxygen lone pair. Second, there is the crucial question of skeletal strain, and, judging from the available information, i.e., that compounds **94**, **100**, and **90a** containing three and four trans double bonds are paratropic, whereas **99** incorporating only two such functions is atropic, it appears that angle-strain effects in the system preclude effective skeletal flattening in frames consisting of less than three trans double bonds.

In terms of Eq. (1), the development of π delocalization in a hetero[15]-annulene may simply be described as a situation in which the stabilizing influence of ΔS_0 (rigidity) overcomes the combined destabilization imparted by ΔH_0^π (antiaromaticity) and ΔH_0^σ (σ strain).

4. Systems with Sixteen π Centers

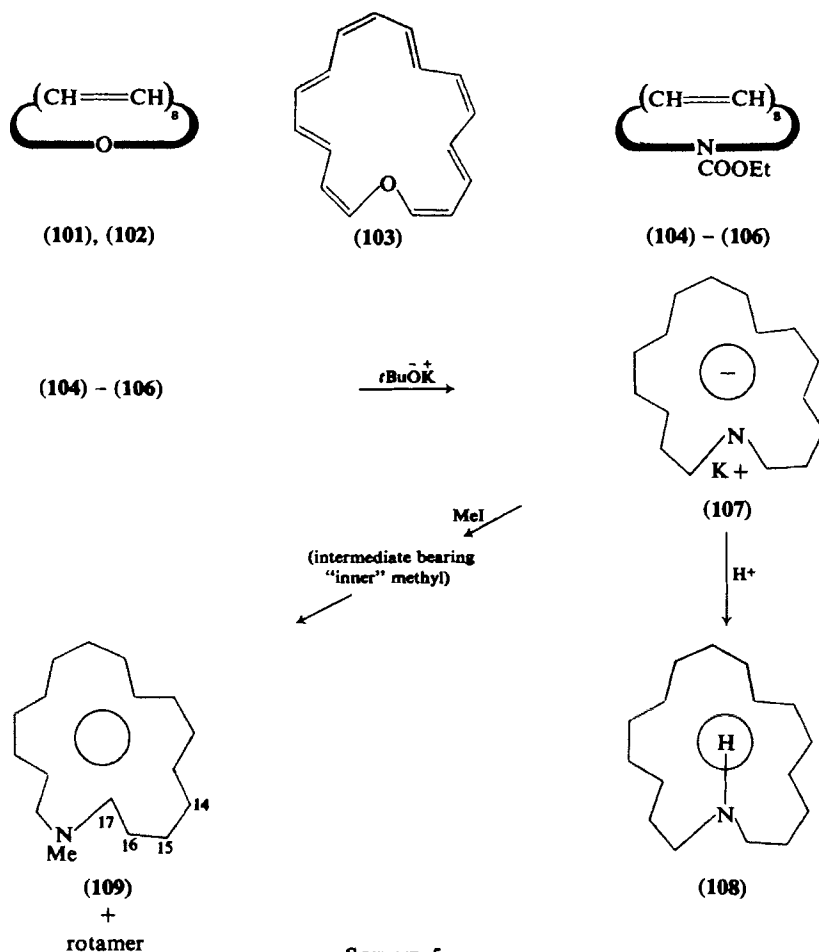
This group of heteroannulenes does not appear to be available at present.

5. Systems with Seventeen π Centers

This family is without doubt the most widely represented of the series, with members existing in a rich variety of structural modifications

ranging from the unconstrained parent to certain triply restricted bridged dehydroannulated analogs.

a. *Parent Hetero[17]annulenes*.⁷⁴ The oxygen and nitrogen prototypes were photosynthesized at -80°C in largely unspecified isomeric forms (101–103⁷⁵ and 104–106,⁷⁶ respectively), starting from a variety of tetracyclic oxiranes and aziridines, i.e., in manner closely analogous to



SCHEME 5

⁷⁴ For a review on the subject, see Schröder.^{64a}

⁷⁵ G. Schröder, G. Plinke, and J. F. N. Oth, *Angew. Chem., Int. Ed. Engl.* **11**, 424 (1972).

⁷⁶ G. Schröder, G. Heil, H. Röttele, and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.* **11**, 426 (1972).

that described earlier in this review for the thirteen-membered ring. The substances described in Scheme 5 bear strong resemblance to the nine- and thirteen-membered counterparts insofar as the system was found to be polyenic in forms such as **101–106** but is rendered distinctly aromatic either by removal of the substituent from **104–106** to yield **107** and **108**^{6a} or by its replacement with an electron-donating variant to produce **109**.⁷⁴ The basic dissimilarity between the two types of unrestricted heteroannulene is illustrated rather strikingly by the NMR information listed in Table VI, the significant upfield shift experienced by the inner-proton resonances observed on passing from oxides (**101–103**) and urethanes (**104–106**) to amines (**108** and **109**) and finally to amide (**107**), pointing unmistakably to the development of ring diamagnetism.

The system's affinity for aromatic mobilization of the loosely held lone pairs present in **107**, **108**, and **109** clearly establishes the existence of sizeable ΔH_0^* terms that are capable of overcoming (i) the pronounced mobility of a seventeen-membered ring and (ii) the development of serious inner-hydrogen strain generated by the presence of four, inwardly directed hydrogens in **107** and five such groups in **108** and **109**.

TABLE VI
SELECT PROTON NMR SHIFTS OF CERTAIN
UNRESTRICTED HETERO[17]ANNULENES^a

Compound	Inner-proton shifts (τ)
101 ^b	4.1–4.8
103 ^b	4.4–5.5
104 , 105 ^c	4.8–6.5
106 ^b	5.0–6.4
108 ^d	7.6–8.5
109 ^d	7.5–9.5
107 ^e	14.9

^a Data from Schröder ^{6a}.

^b Spectrum recorded in CS₂/THF-d₈ at –100°C.

^c Spectrum recorded in CS₂ at –60°C.

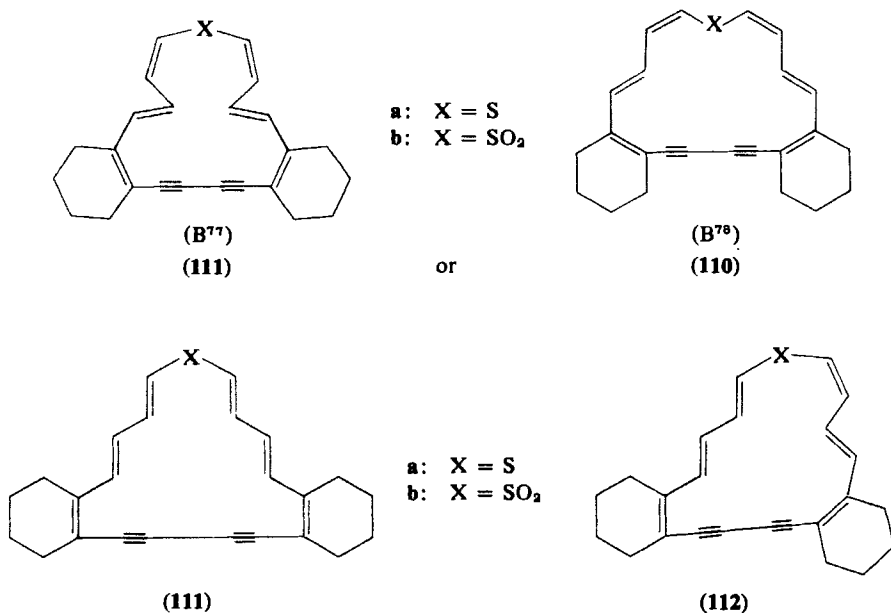
^d Spectrum recorded in CS₂ at 25°C.

^e Spectrum recorded in THF at 25°C.

b. *Restricted Hetero[17]annulenes*. Partial reduction of the system's skeletal mobility and in-cavity strain was accomplished by the commonly practiced, synthetically convenient, replacement of two consecutive ethylenic functions by a bisacetylene group. The members of this

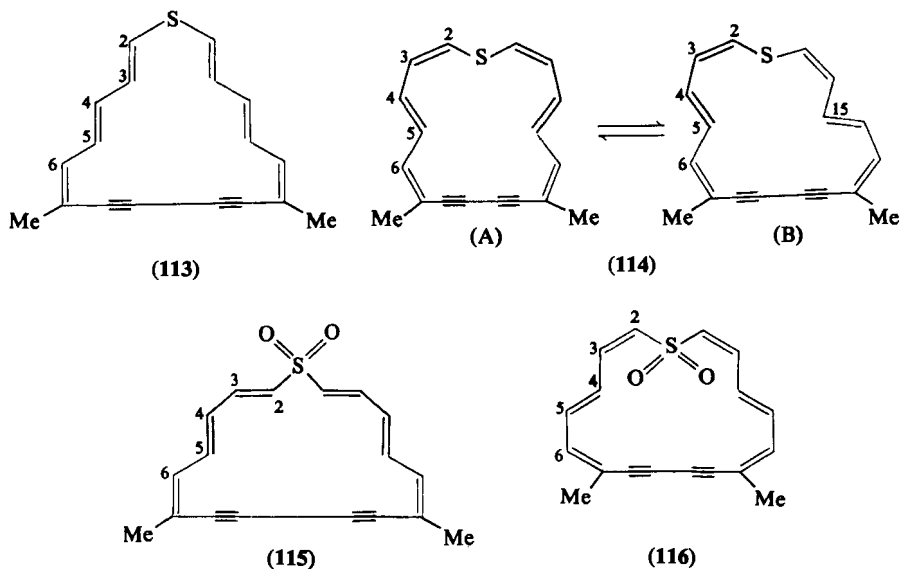
restricted family of heteroannulenes are strictly sulfur-containing molecules made available by the proper use of Wittig reagent (**45b**) and shown in structures **110–116**.^{77,78} Extensive NMR analysis of the annulated derivatives **110**, **111**, and **112**, including direct comparison with appropriate acyclic models in the case of **110a** and **b** has led to the classification of the tetra-*trans*-sulfide (**111a**) as diatropic, the di-*trans*-sulfone (**110b**) as paratropic, and the remaining variants as largely atropic.⁷⁷ This description appears to be basically sound, although a more recent study conducted on the methylated analogs of the family (**113–116**)⁷⁸ has shown the basic molecular frame of the di-*trans* isomer to be conformationally mobile, thus raising the possibility that the absence of a ring current in sulfides such as **110a** and, possibly, **112a** may well be due to rapid thermal interconversion between two or more rotationally isomeric forms at room temperature.

Specifically, what was observed by examining a properly dideuterated variant of **114** by variable-temperature ¹H NMR is that the molecule is conformationally mobile and atropic at ambient temperature but “freezes” into a nearly equal mixture of the two diatropic rotamers,



⁷⁷ R. H. McGirk and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **11**, 834 (1972).

⁷⁸ R. L. Wife and F. Sondheimer, *Tetrahedron Lett.*, 195 (1974).



formulated as **114(A)** and **114(B)** upon cooling to -75°C . By contrast, the NMR spectra of sulfide (**113**) and sulfones (**115** and **116**) were found to be temperature-invariant, although in the case of **113** the NMR shifts of the trans unit directly linked to sulfur were actually rationalized in terms of rotational mobility. Judged strictly on the basis of internally consistent, proton shift differences (the ^1H NMR spectra of proper acyclic models do not appear to be available here for direct comparison), sulfide (**113**) was characterized as diatropic and sulfones (**115** and **116**) were, respectively, classified as atropic and paratropic. Some salient NMR information that was utilized in the classification of the various bisdehydrothia-annulenes (**110–116**) is listed in Table VII. The tabulated data are seen to be internally consistent with the specified classification, although the rather dramatic downfield shift experienced by the inner protons of sulfones (**110b** and **116**) may be due largely to the influence of the in-cavity oxygen functions. Despite this possible effect, however, it must be noted that the methyl signals and outer-proton resonances (not listed in Table VII) do experience meaningful upfield shifts on passing from **111b** and **115** to **110b** and **116** so that the latter pair of sulfones may safely be classed as paratropic relative to the former.

In concluding the discussion on these partially constrained members of the family it may be well to stress that the temperature-dependent development of diatropicity in **114**, and possibly **110a** as well, properly illustrates the sometimes crucial influence that $T\Delta S_0$ exerts in Eq. (1).

TABLE VII
PROTON NMR SHIFTS OF CERTAIN RESTRICTED THIA[17]ANNULENES^a

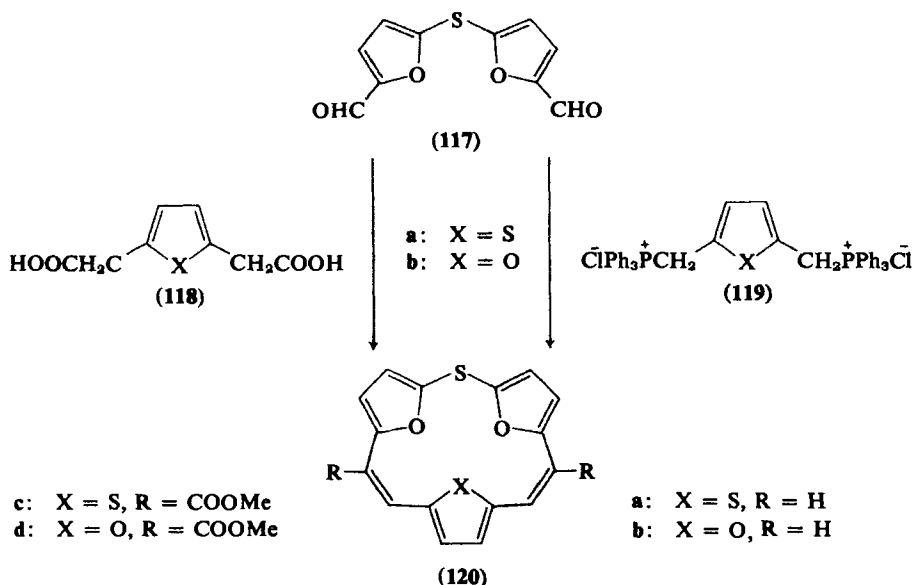
Compound	Proton shift (τ)						Methyl
	H ²	H ³	H ⁴	H ⁵	H ⁶	H ¹⁵	
113 ^b	4.42	4.85	3.09	5.63	2.81	—	7.78
114 ^b	3.01	3.45	3.61	4.42	3.11	—	7.78
114(A) ^c	—	—	—	5.21	—	—	—
114(B) ^c	—	—	—	5.37	—	4.39	—
115 ^b	4.57	2.81	3.37	4.17	3.10	—	7.90
116 ^b	4.40	3.71	-0.60	~4.2	4.16	—	8.20

^a Data from Wife and Sondheimer.⁷⁸

^b Spectrum recorded in CDCl₃.

^c Spectrum recorded in THF-d₈ at -75°C.

The tris heterobridged thia[17]annulene (120) is available in unsubstituted as well as diester form from base-induced ring-forming condensation between dialdehyde 117 and 118 or 119, respectively.⁷⁹ Analysis of the unsubstituted system 120a and b by ¹H NMR revealed both members to be atropic. Rationalizations of this result center chiefly on (i) the



⁷⁹ T. M. Cresp and M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1786 (1973).

large size of the thiophene sulfur in **120a**, which is believed to prevent the molecule's periphery from attaining the necessary planarity, and (ii) the tendency of the furan rings in **120b** to inhibit the development of 18π peripheral delocalization through a stronger, locally sustained, 6π effect. Further, NMR comparisons between **120** and the iso- π -electronic carbocycle, i.e., the molecule in which the sulfur atom of **120** is replaced by a double bond, or the corresponding annulenone, i.e., **120** with CO in place of sulfur, have led to the general conclusion that the ring current in thia-annulenes appears to be less than in either annulenes or annulenones of comparable ring size.⁷⁹

Besides being the largest, unrestricted, π -excessive rings currently in existence, the hetero[17]annulenes also represent the smallest ring system to be made available in the triply restricted bridged bisdehydroannulated form formulated in **123**⁸⁰⁻⁸² and **126**.^{83,84} As shown in the preparation of compounds **123** and **126**, initial entry into the basic skeleton was gained by properly designed Wittig condensation. Conversion of the initial acyclic diacetylenic substances, thus obtained, into the desired skeleton was successfully realized by a sequence of steps consisting of base-induced reduction and oxidative terminal acetylene coupling.

Because of their highly rigid frames, the resulting bridged bisdehydroannulated hetero[17]annulenes are associated with a highly favorable ΔS_0 term. In addition, the presence of (i) a linearly disposed, "bare," diacetylene function and (ii) four trans double bonds, two of which are devoid of inner hydrogens, provides the molecule with a rather large cavity and a skeleton that is relatively low in both angle and inner-proton strain, i.e., one in which the destabilizing effect of ΔH_0^σ ought not to be particularly serious. As a result of the stated structural characteristics, the general frames shown in **123** and **126** are ideally suited for sustaining peripheral delocalization. In fact, it is not unreasonable to expect the development of a π -delocalized frame in these substances even in cases where electron mobility is known to be effectively inhibited in the less constrained analogs by heteroatom electronegativity, as in **101-106** for example.

Brief examination of the selected NMR information, relating to the chemical shifts of inner and bridge protons, presented in Table VIII, reveals this to be precisely the case. It is thus seen that the system does

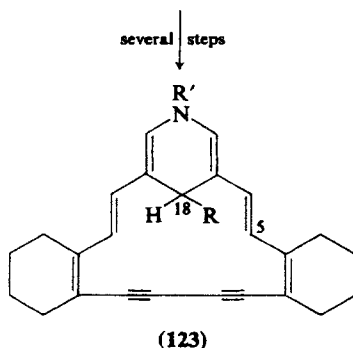
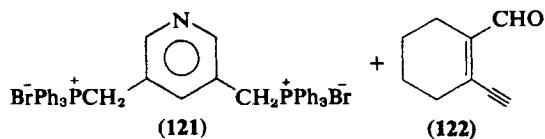
⁸⁰ P. J. Beeby and F. Sondheimer, *J. Am. Chem. Soc.* **94**, 2128 (1972).

⁸¹ P. J. Beeby and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **11**, 833 (1972).

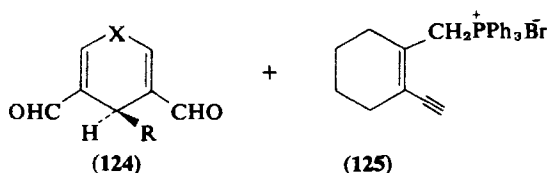
⁸² P. J. Beeby, J. M. Brown, P. J. Garratt and F. Sondheimer, *Tetrahedron Lett.*, 599 (1974).

⁸³ J. M. Brown and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **13**, 337 (1974).

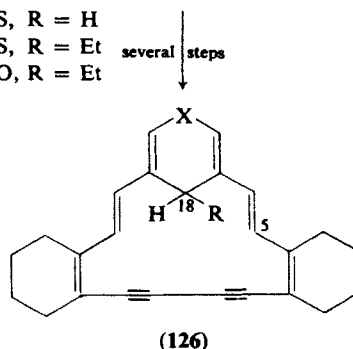
⁸⁴ J. M. Brown and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **13**, 339 (1974).



- a: $R' = K^+$, $R = H$
 b: $R' = K^+$, $R = \text{alkyl}$
 c: $R' = H$, $R = H$
 d: $R' = H$, $R = \text{alkyl}$
 e: $R' = \text{Me}$, $R = H$
 f: $R' = \text{Me}$, $R = \text{alkyl}$
 g: $R' = \text{COMe}$, $R = H$
 h: $R' = \text{COOEt}$, $R = H$



- a: $X = S$, $R = H$
 b: $X = S$, $R = \text{Et}$
 c: $X = O$, $R = \text{Et}$



- a: $X = S$, $R = H$
 b: $X = S$, $R = \text{Et}$
 c: $X = O$, $R = \text{Et}$
 d: $X = \text{SO}_2$, $R = H$
 e: $X = \text{SO}_2$, $R = \text{Et}$
 f: $X = \text{syn-SO}$, $R = \text{Et}$
 g: $X = \text{anti-SO}$, $R = \text{Et}$

sustain a ring current and, more important, that its ability to do so is not limited to the amides, amines, and sulfides, but also extends to such variants as acetamide (**123g**), urethane (**123h**), and oxide (**126c**), whose lone pairs normally resist mobilization. As expected, the magnitude of the ring current was shown to be inversely related to heteroatom electronegativity, the molecule's diatropicity decreasing in the order $N^-K^+ \gg \text{NMe} \sim \text{NH} > \text{S} > \text{NCOOEt} > \text{NAc} \sim \text{O}$. The data listed in Table VIII also reveal the members lacking a heteroatomic lone pair to be

TABLE VIII
SELECTED PROTON NMR SHIFTS OF CERTAIN HEAVILY RESTRICTED
HETERO[17]ANNULENES AND RELATED MODELS^a

Compound	Chemical shifts (τ) ^{b,c}	
	Inner proton (H ^a)	Bridge proton (H ¹⁸)
123a	11.51	14.24
123e	7.33 (+4.08)	10.83 (+3.97)
123c	6.99 (+3.73)	10.55 (+3.70)
123h	4.78 (+1.72)	8.77 (+1.86)
123g	4.51 (+1.54)	8.54 (+1.68)
126a	5.22 (+2.25)	8.98 (+2.26)
126c	4.27 (+1.43)	—
126d	1.33 (−1.21)	5.63 (−0.90)
126f	1.01 (−1.56)	4.63 (−1.60)
126g	2.18 (−0.43)	5.41 (−0.58)

^a Data from Sondheimer and co-workers.^{80-84.}

^b Parenthesized values denote differences in chemical shift between a given annulene (**123** or **126**) and its acyclic model.

^c Recorded in THF- d_6 for **123a** and in $CDCl_3$ for **123c,e,h,g**, **126a,c,d,f,g**.

distinctly paratropic in the case of sulfone (**126d**) and *syn*-sulfoxide (**126f**) but essentially atropic in the case of *anti*-sulfoxide (**126g**). The paratropic character of **126d** and **126f** was attributed⁸⁴ to the development of an 18π -electron Möbius antiaromatic system believed to arise from interaction between the π system of the carbocyclic portion of the molecule's periphery and a properly directed 2p electron pair on oxygen; the *anti*-sulfoxide (**126g**), being sterically incapable of offering its oxygen unit for such interaction, remains atropic.

The information described in this section allows one to conclude that, irrespective of skeletal restriction, the development of conventional temperature-independent Hückel delocalization in the hetero[17]-annulenes requires the presence of four trans double bonds. The situation is exemplified by **107** and **108** for the unrestricted case, by **113** for the partially restricted case, and by **123** for the heavily restricted case.

6. Systems with Eighteen π Centers

Information about this group of compounds appears to be lacking at the present time.

7. Systems with Nineteen π Centers

Apparently, the potentially antiaromatic (20π) nineteen-membered heteroannulene frame is known to exist only as the highly constrained urethane shown in **130** which was synthesized⁸⁵ from **127** and **128** by a sequence similar to that described for the more symmetrical seventeen-membered analogs.

Although **130** is undoubtedly less rigid than its lower double-bond homolog (**123h**), skeletal motion must still be sufficiently restricted so

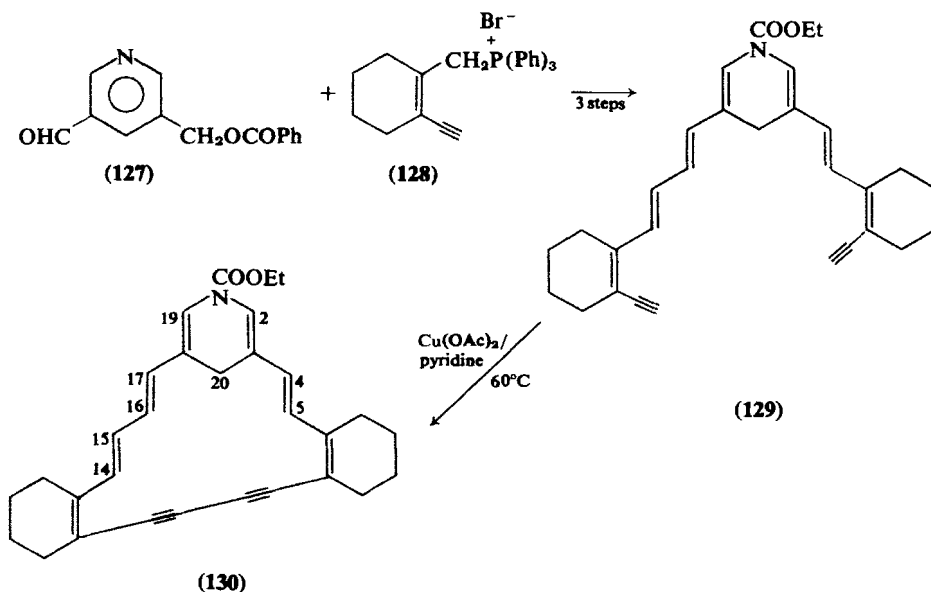


TABLE IX

PROTON NMR SHIFTS OF AZA[19]ANNULENE (**130**) AND ITS ACYCLIC MODEL (**129**)^a

Compound	Chemical shifts (τ) ^b							
	$\text{H}^2, \text{H}^{19}$	H^4	H^5	H^{14}	H^{15}	H^{16}	H^{17}	H^{20}
130	3.42	4.00	1.20	0.86	4.05	1.79	4.10	5.37
129	3.00	3.58	3.10	2.98	3.55	3.65	3.65	6.93
Δ (130 - 129)	+0.42	+0.42	-1.9	-2.12	+0.50	-1.86	+0.45	-1.56

^a Data from Beeby and Sondheimer.⁸⁵^b Recorded in CDCl_3 .⁸⁵ P. J. Beeby and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **12**, 411 (1973).

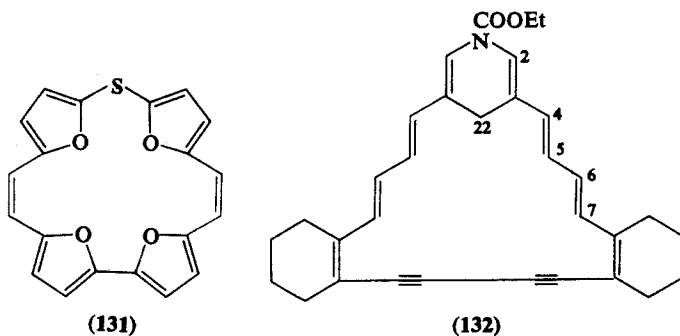
that the molecule may be expected to be associated with a highly favorable ΔS_0 term, which, as was indicated earlier, is a necessary condition for lone-pair participation in antiaromatic delocalization. This, in fact, turns out to be the case, as brief examination of the proton NMR shifts listed in Table IX reveals **130** to be paratropic, its outer and inner proton resonances, respectively, appearing above and below normal.

8. Systems with Twenty π Centers

Members of this family do not appear to be available.

9. Systems with Twenty-one π Centers

There are two known representatives of this group, the tetra-bridged thia-annulene (**131**)⁷⁹ and the triply restricted urethane (**132**)⁸⁶ which were prepared by procedures analogous to those described previously for **120b** and **123**, respectively. Of the two, **131** was found not to sustain a ring current, whereas **132** was shown to be diatropic. The atropic nature of **131** has been attributed to the perturbation introduced to peripheral π mobility by the locally sustained 6π effect contributed by each of the four bridging furan rings. The factors believed to be responsible for the development of ring diamagnetism in **132** are essentially the



same as those previously discussed at some length in connection with the seventeen-membered $(4n + 2)\pi$ homolog (**123h**). Nonetheless, direct comparison in terms of the NMR information listed in Table X reveals the ring current of the larger member, i.e., **132**, to be significantly less developed. Based on this observation, it was concluded that "diamagnetic ring current effects in $(4n + 2)\pi$ -electron systems become less as

⁸⁶ P. J. Beeby and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **12**, 410 (1973).

the size of the macrocyclic ring is increased.”⁸⁶ Although this interpretation is basically sound, one must exercise caution not to attribute the observed ring-current differences between **123h** and **132** solely to a change in the system's π -electron potential for delocalization, as given by ΔH_0^π in Eq. (1), without due regard to possible variations in ΔH_0^σ and ΔS_0 as well. In fact, bearing in mind that the change from **123h** to **132** must, for obvious reasons, (i) enhance the system's skeletal flexibility and (ii) increase the degree of in-cavity proton strain,⁸⁷ one may reasonably view the reduction of ring current attending the change from seventeen- to twenty-one-membered heteroannulene primarily, if not exclusively, as being the result of increased influence exerted by the $\Delta H_0^\sigma - T\Delta S_0$ combination in Eq. (1).

TABLE X
PROTON NMR SHIFTS OF AZA[21]ANNULENE (**132**) AND ITS ACYCLIC MODEL^a

Compound	Chemical shifts (τ) ^b					
	H ²	H ⁴	H ⁵	H ⁶	H ⁷	H ²²
132	2.58	3.17	4.61	3.10	4.10	8.00
Model ^c	3.02	3.62	3.62	3.53	2.95	6.94
Δ (132 -model)	-0.43	-0.45	+1.00	-0.43	+1.15	+1.06

^a Data from Beeby and Sondheimer.⁸⁸

^b Recorded in CDCl₃.

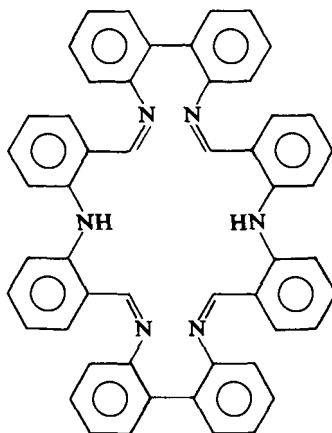
^c Compound similar to **132** but lacking the bond linking the two acetylenic units.

10. Systems with More than Twenty-one π Centers

The only representative of this macrocyclic group of molecules is a hexaaza derivative believed to possess the heavily annulated structure shown in **133** and formed quantitatively on reaction of 2,2'-diaminobiphenyl with diphenylamine-2,2'-dicarboxyaldehyde.⁸⁸ From the limited

⁸⁷ The increase in the degree of in-cavity proton crowding attending the change from planar hetero[17]annulene (**123h**) to the twenty-one-membered counterpart (**132**) despite the latter's wider cavity becomes evident from an examination of Dreiding molecular models. Specifically, one measures the following in-cavity non-bonded distances: H⁵-H¹⁴ \sim 2.9 Å and H⁵- or H¹⁴-*syn*-H¹⁸ \sim 1.7 Å for **123h** and H⁵-H¹⁸ \sim 2.5 Å, H⁷-H¹⁸ \sim 4.0 Å, H⁵-H⁷ and H¹⁶-H¹⁸ \sim 2.4 Å, and H⁵-*syn*-H²² \sim 1.4 Å for **132**.

⁸⁸ I. Agranat, *Tetrahedron* **29**, 1399 (1973).



(133)

NMR information available on **133**, it is not possible to judge whether or not the molecule sustains a ring current along its twenty-six-membered perimeter. Even if the question of ring current in **133** could be resolved, however, it is obvious that the serious perturbation introduced by benzoannulation effectively precludes the formulation of any conclusions concerning the electronic nature of the basic π frame surrounding the cavity.

III. Concluding Remarks

Although less than a decade old, the bulk of the experimental information now available on the subject of heteroannulene chemistry is sufficiently advanced to permit meaningful generalizations concerning the basic requirements for the development of lone-pair-induced π delocalization.

The first and, possibly, the most intuitively satisfying among these concerns the nature of the lone pair and the fact that its participation into the π system bears unmistakable dependence on its mobility as controlled by the effective electronegativity of its heteroatomic host, the unit's suitability as a double-bond substitute decreasing in the order $N^- > NH \sim N\text{Alkyl} > S > N\text{Acyl} > O$. It is further noted that this heteroatom-electronegativity effect is most spectacularly manifested in the "unrestricted" members of the $(4n + 2)\pi$ series such as the nine-, thirteen-, and seventeen-membered rings where a change between the

two heteroatomic extremes listed above, i.e., N^- to O, serves to transform the system from planar and extensively delocalized, as in **27**, **77** (**81**), and **107**, to heavily buckled and localized as in **24a**, **74** (**75** or **76**) and **101** (**102**, **103**).

Second, the ability of a heteroannulene to exist in planar form is seen to depend on molecular size and, within a specified size, on the relative number of cis and trans double bonds and the sequence in which these groups occur. Basically, the influence of skeletal strain here is the same as that deduced previously for the carbocyclic analogs. Specifically, one finds the nine-membered system, the heteronins, to be the largest member of the family capable of attaining planarity while in possession of an all-cis perimeter, the development of a flat frame in the larger members requiring the presence of an ever-increasing number of trans bonds with increasing ring size.

Third, there is ample indication that the increased rigidity of the heavily "restricted" heterocyclic perimeters significantly relaxes the requirement of high lone-pair mobility for the development of π delocalization. It is notable, for example, that such heavily constrained perimeters as the oxa[17]annulene (**126c**), the aza[17]annulenes (**123g** and **h**), and the aza[21]annulene (**132**) show clear signs of diatropicity despite the fact that they all incorporate highly electronegative heteroatoms bearing lone pairs that are known effectively to resist delocalization in the corresponding unrestricted environment, e.g., **101** (**102**, **103**) and **104** (**105**, **106**), respectively, for the seventeen-membered case. The controlling influence that skeletal rigidity has on the mobilization of lone pairs is perhaps best exemplified by the actual development of "antiaromatic" (paratropic) delocalization in the heavily restricted fifteen- and nineteen-membered $(4n)\pi$ systems depicted in **90a** and **130**.

Finally, judging from all the information currently in hand, it may be deduced that replacement of two or more double bonds by heteroatomic π -excessive units, as in the diheterocins described in Section II,B,1, the triheteronins (**52**), and the dithia[10]annulene (**53**), significantly reduces lone-pair mobility chiefly as a result of enhanced electron repulsion.

By way of general conclusion it is perhaps worth stressing that all information now available on the heteroannulenes serves unequivocally to establish that the notion of a lone pair replacing a double bond in the development of π delocalization is a realistically sound one having received experimental verification in a variety of structural environments widely differing in size and shape.

Advances in Indolizine Chemistry

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I. Introduction

The heterocyclic nucleus, pyrrolo[1,2-*a*]pyridine, has been known in the chemical literature by several names including pyrindole, pyrrodine, and pyrrocoline, but the one which is now used by *Chemical Abstracts*, and which will be used throughout this review, is indolizine. The numbering of this system is shown in Fig. 1.

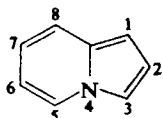


FIG. 1. The numbering system for indolizine.

Indolizine is an important ring system in view of its similarity to indole. Like indole, it has a delocalized 10π -electron system that confers aromaticity, in contrast to its analogs, pyrrolizine and quinolizine. Consequently, it has a theoretical and practical interest.

Apart from academic interest in its synthesis and properties, most of the work on indolizine has been concerned with the search for drugs (e.g., synthesis of indolizine analogs of indole derivatives which are widely distributed in nature), for dyestuffs, and for light-screening agents in photographic emulsions.

Although the indolizine nucleus appears not to occur naturally, its perhydro derivative, commonly named indolizidine, is the alkaloid δ -coniceine, and this nucleus is to be found in several groups of alkaloids including those from the plant groups *Ipomoea*, *Elaeocarpus*, *Tylophora*, *Amaryllidaceae*, and *Orchidaceae*. Since the chemistry of these alkaloids has been reviewed regularly,¹ only selected examples will be taken from the natural products field.

¹ R. H. F. Manske and H. L. Holmes, eds., "The Alkaloids," Vol. 2, Chapter 5. Academic Press, New York, 1952.

Indolizines and their partially or wholly reduced derivatives were comprehensively reviewed in 1948 by Borrows and Holland.² They were subsequently mentioned by Elderfield³ in 1952 and in more detail in 1961 by Mosby⁴ covering the literature up to the middle of 1958. The present review covers developments in indolizine and indolizidine chemistry since that time and includes publications listed in *Chemical Abstracts* up to the end of February 1977.

A general review of indolizines has recently been published in a Russian journal⁵ and, additionally, reviews of synthetic routes have also appeared.^{6,7}

II. Synthetic Routes to Indolizines

A. THE TSCHITSCHIBABIN AND CLOSELY RELATED REACTIONS

This synthesis, originally devised by Tschitschibabin,⁸ is still the most widely used because it can easily be modified to yield substituted indolizines. The synthesis involves the quaternization of a 2-substituted pyridine, normally using an α -halo carbonyl compound, followed by intramolecular cyclization of the quaternary salt with a mild base, usually aqueous sodium bicarbonate (Scheme 1).

Although the cyclization normally proceeds directly to the indolizine, the carbinol intermediate (**1**) was the product isolated when 2-picoline and 2-bromopropiophenone were heated together in the absence of a solvent.⁹ Usually the intermediate quaternary salt is isolated, but in some cases this is unnecessary and only the final product is isolated^{10,11} e.g., the base **2** in Eq. (1). A similar reaction, using an α -bromoester

² E. T. Borrows and D. O. Holland, *Chem. Rev.* **42**, 611 (1948).

³ H. R. Ing, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3, Chapter 5. Wiley, New York, 1952.

⁴ W. L. Mosby, in "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Part 1. Interscience, New York, 1961.

⁵ N. S. Prostakov and O. B. Baktibaev, *Usp. Khim.* **44**, 1649 (1975).

⁶ T. Uchida and K. Matsumoto, *Synthesis* **4**, 209 (1976).

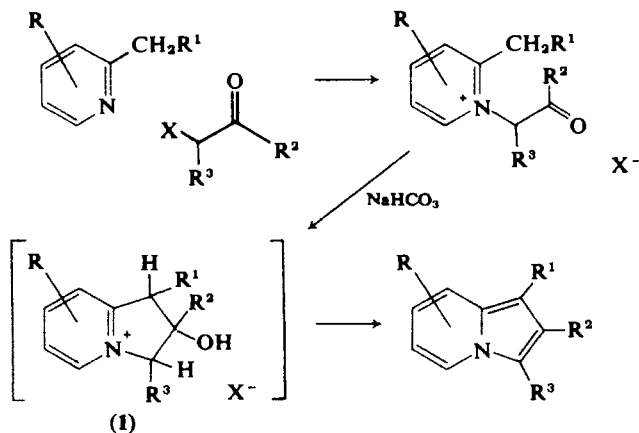
⁷ K. Matsumoto, *Yuki Gosei Kagaku Kyokai Shi* **32**, 731-748 (1974) [*CA* **82**, 72665 (1975)].

⁸ A. E. Tschitschibabin, *Ber. B* **60**, 1607 (1927).

⁹ E. E. Glover, K. D. Vaughan, and D. C. Bishop, *J. Chem. Soc., Perkin Trans. 1*, 2595 (1973).

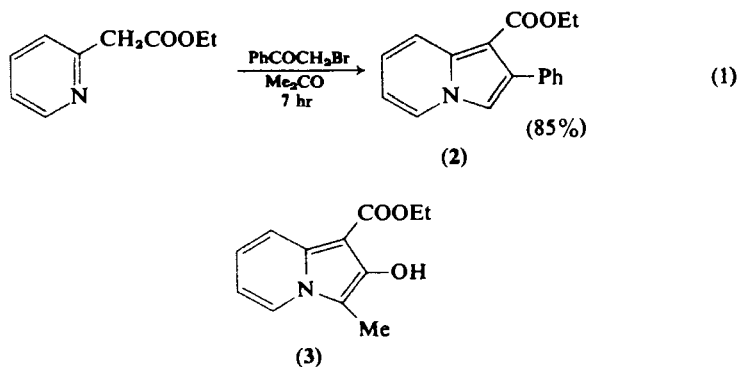
¹⁰ D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 2627 (1962).

¹¹ W. Engel, E. Seeger, H. Teufel, and A. Eckenfels, *Ger. Offen.* 1,922,191 (1970) [*CA* **74**, 12995 (1971)].



SCHEME 1

instead of an α -bromoketone, gave 3, the first reported 2-hydroxy-indolizine.¹²



However, most of the reported cyclizations of the type of Scheme 1 have utilized an α -halo-(usually bromo)ketone as the quaternizing agent. The R^2 may be aliphatic¹³⁻¹⁵ but is more often aromatic¹⁶⁻²³ or hetero-

¹² D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 3277 (1963).

¹³ J. Bailey and D. G. Dalton, *British Patent* 1,156,495 (1969) [*CA* 71, 81216 (1969)].

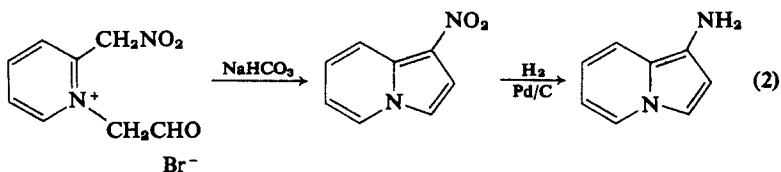
¹⁴ N. S. Prostakov and O. B. Baktibaev, *Khim. Geterotsikl. Soedin.* 7, 1395 (1971) [*CA* 76, 46061 (1972)].

¹⁵ C. Casagrande, A. Invernizzi, R. Ferrini, and G. Miragoli, *Farmaco, Ed. Sci.* 26, 1059 (1971) [*CA* 76, 85660 (1972)].

¹⁶ E. E. Mikhлина, A. D. Yanina, T. S. Loseva, K. F. Turchin, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 977 (1974) [*CA* 82, 16671 (1975)].

cyclic.²⁴⁻²⁷ The latter reactions especially, proceed in high yield, and the products are usually stable solids. By variation of R¹, many novel indolizines have been prepared,²⁸ including 1-cyano, 1-amino, and 1-hydroxy compounds.²⁸⁻³⁰

The synthesis of hydroxy- and aminoindolizines has been examined in some detail.³⁰ The reaction of 2-(nitromethyl)pyridine and bromoacetaldehyde gave 1-nitroindolizine, which was reduced to the corresponding amino compound [Eq. (2)].



Although 1-aminoindolizine could be diazotized and coupled with β -naphthol, both the base and its hydrochloride salt were air- and light-sensitive. Various substituted 1-aminoindolizines have been prepared via a Tschitschibabin reaction from substituted 2-nitromethyl- or 2-acetamidomethylpyridines.³¹ The 1-hydroxy-2-phenylindolizine prepared from 2-hydroxymethylpyridine and phenacyl bromide was isolated as its hydrochloride, but this too was unstable and was characterized as the *O*-benzoyl derivative.

A 1-nitroindolizine was obtained by ring closure of the quaternary salt **4** with nitromethane³² [Eq. (3)]. Presumably a Tschitschibabin

¹⁷ E. A. Kochetkova, *Zh. Obshch. Khim.* **33**, 1201 (1963) [*CA* **59**, 9978 (1963)].

¹⁸ V. S. Venturella, *J. Pharm. Sci.* **52**, 868 (1963).

¹⁹ K. R. Kallay and R. F. Doerge, *J. Pharm. Sci.* **61**, 949 (1972).

²⁰ N. P. Buu-Hoi, M. Delcey, P. Jacquignon, and F. Perin, *J. Heterocycl. Chem.* **5**, 259 (1968).

²¹ I. Dainis, *Aust. J. Chem.* **25**, 1003 (1972).

²² L. Petit and P. Touratier, *Bull. Soc. Chim. Fr.* **8**, 2529 (1966).

²³ N. P. Buu-Hoi, F. Perin, and P. Jacquignon, *J. Heterocycl. Chem.* **2**, 7 (1965).

²⁴ N. Saldabols, L. N. Alekseeva, B. Brizga, L. Kruzmetra, and S. Hillers, *Khim.-Farm. Zh.* **4**, 20 (1970) [*CA* **73**, 77136 (1970)].

²⁵ G. Vasiliu and E. Cohn, *An. Univ. Bucuresti, Ser. Stiint. Nat. Mat.-Mec.* **12**, 133 (1963) [*CA* **65**, 7171 (1966)].

²⁶ F. Kröhnke and K. F. Gross, *Chem. Ber.* **92**, 22 (1959).

²⁷ A. F. Oleinik, G. A. Modnikova, K. Yu. Novitskii, T. A. Gus'kova, and G. N. Pershin, *Khim.-Farm. Zh.* **8**, 7 (1974) [*CA* **81**, 63554 (1974)].

²⁸ L. A. Walter, U.S. Patent 3,642,807 (1972) [*CA* **76**, 140563 (1972)].

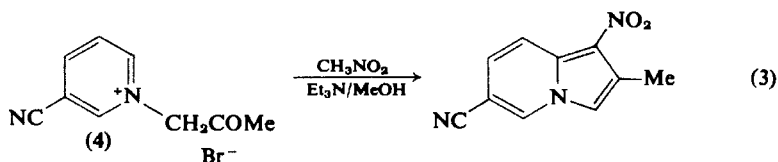
²⁹ K. Ogata, *Yakugaku Zasshi* **89**, 1020 (1969) [*CA* **71**, 101636 (1969)].

³⁰ J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 2948 (1965).

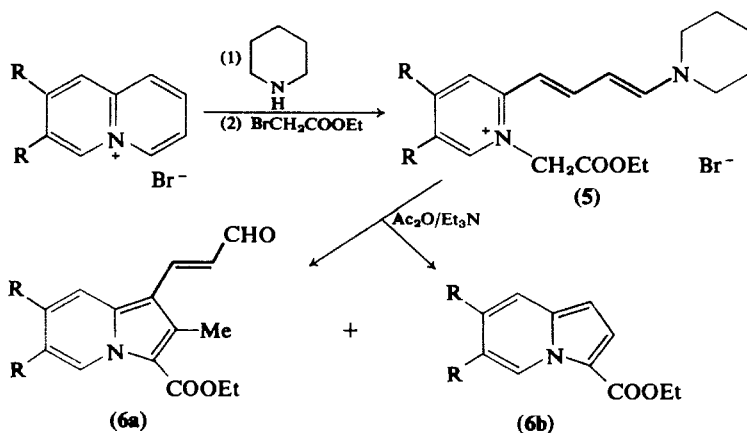
³¹ T. Melton and D. G. Wibberley, *J. Chem. Soc. C*, 983 (1967).

³² W. Kiel and F. Kröhnke, *Chem. Ber.* **105**, 3709 (1972).

reaction follows nitromethylation with oxidation at some stage. This method has been applied mainly to the cyclization of quaternary salts of quinolines and isoquinolines to form benzindolizines.



Quinolizinium salts can be cleaved by a secondary amine such as piperidine and the resulting tetramethine compounds **5** can be converted into indolizines **6** as shown in Scheme 2.^{33,34}



SCHEME 2

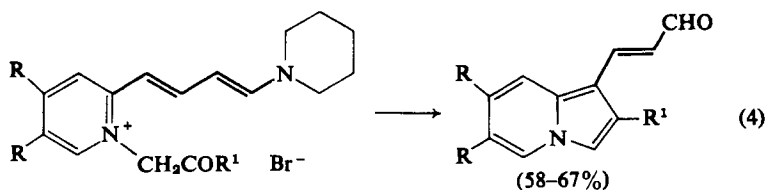
The ratio of the products **6a** and **6b**, which were originally incorrectly formulated but later corrected³⁵ on the basis of NMR data, varies with the duration and temperature of the reaction: **6a** predominates after 2 days at 40°C, **6b** after 6 weeks at 0°C.

If an α -bromoketone was used instead of the α -bromo ester of Scheme 2, the quaternary salts could be cyclized on an alumina column [Eq. (4)].

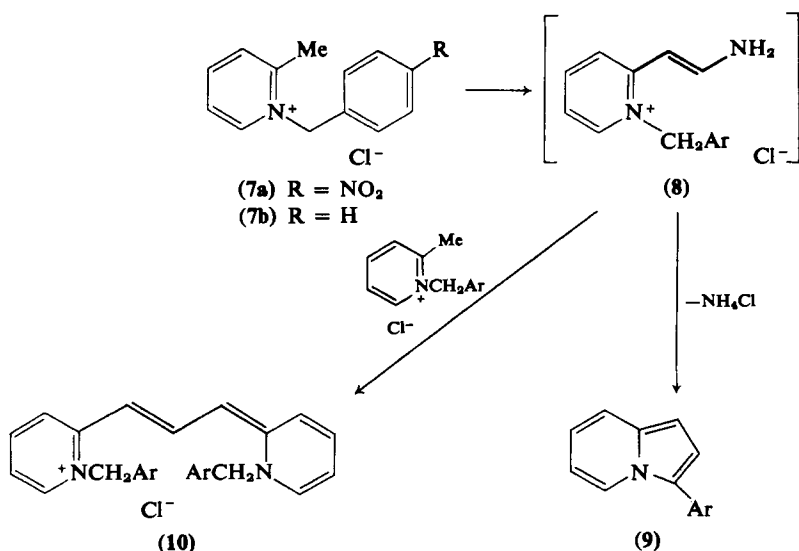
³³ F. Kröhnke and D. Moerler, *Tetrahedron Lett.*, 3441 (1969).

³⁴ F. Kröhnke and D. Moerler, *Ann.* **744**, 65 (1971).

³⁵ F. Kröhnke, *Tetrahedron Lett.*, 2607 (1972).



Kreutzberger and Abel³⁶ showed that treatment of *p*-nitrobenzyl- α -picolinium chloride (**7a**) with *s*-triazine in pyridine gave an 8% yield of the cyclized indolizine (**9**), presumably via the resonance-stabilized intermediate **8** (see Scheme 3).



SCHEME 3

The trimethine dye (**10**) was also obtained in slightly greater yield, and since the less activated benzyl quaternary salt (**7b**) gave only the trimethine compound (in 59% yield), this would not appear to be a practical route to the indolizine. (Ethyl orthoformate and **7a** in the presence of piperidine gave **9** in 67% yield).

In a reaction somewhat similar to that of Tschitschibabin, *N*-propargyl-2-picolinium bromide was cyclized by base to 2-methylin-dolizine, but the yield was poor compared to that of the 1-aza analog prepared by a similar route.^{37,38}

³⁶ A. Kreutzberger and D. Abel, *Arch. Pharm. (Weinheim)* **302**, 701, (1969).

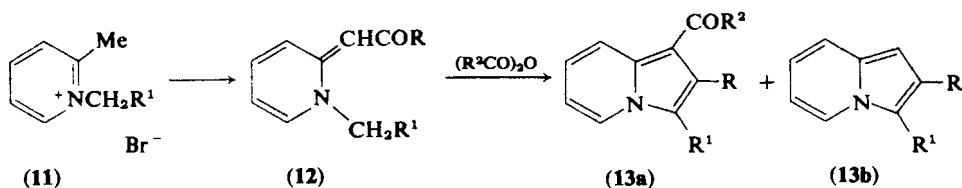
³⁷ I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* **11**, 1564 (1963).

³⁸ Sankyo Co. Ltd., Japanese Patent 22,262 (1965) [*CA* **64**, 2568 (1966)].

B. INTRAMOLECULAR CYCLIZATIONS USING ACETIC ANHYDRIDE

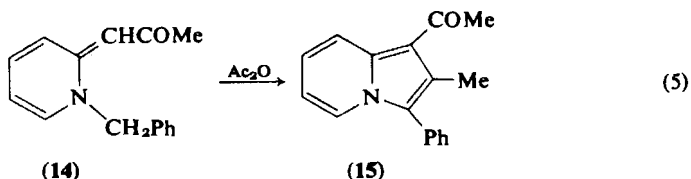
The original Scholtz synthesis of indolizine³⁹ was based on the reaction of 2-picoline with acetic anhydride; his intermediate "picolide" has been shown to be 1,3-diacetylundolizine.⁴⁰

Although this method is rarely used because of the poor yields often associated with it, acetic and other anhydrides have been shown to promote the formation of indolizines from pyridine quaternary salts in a cyclization reaction in which the 2,3-bond of the indolizines is formed.^{31,41-45} This route starts from a quaternary salt of general formula **11** which is acylated and dehydrobrominated in one step to give **12**. Heating **12** under reflux with acetic anhydride gives the indolizine **13a** or **13b** (Method A) (see Scheme 4).³¹ Alternatively, the quaternary salt can be converted directly into the indolizine by employing triethylamine (Method B).⁴¹ Some idea of the scope of the reaction can be gained from Table I.



SCHEME 4

In favorable cases, the reaction gives good yields of the 1-acyl-indolizine **13a**. However, where either the carbonyl or $\text{—N}^+\text{CH}_2\text{—}$ group is not sufficiently activated, unexpected products are formed [e.g., **14** \rightarrow **15** but **16** \rightarrow **17**; Eqs. (5) and (6)]. Both Melton and Wibber-



³⁹ M. Scholtz, *Ber.* **45**, 734 (1912).

⁴⁰ V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.* **82**, 1456 (1959).

⁴¹ T. Melton, J. Taylor, and D. G. Wibberley, *J. Chem. Soc. Chem. Commun.*, 151 (1965).

⁴² F. W. Kröck and F. Kröhnke, *Chem. Ber.* **102**, 669 (1969).

⁴³ F. W. Kröck and F. Kröhnke, *Chem. Ber.* **102**, 659 (1969).

⁴⁴ I. Dainis, *Aust. J. Chem.* **25**, 1025 (1972).

⁴⁵ N. S. Prostakov and O. B. Baktibaev, *Khim. Geterotsikl. Soedin.*, 1220 (1972) [*CA* **77**, 164401 (1972)].

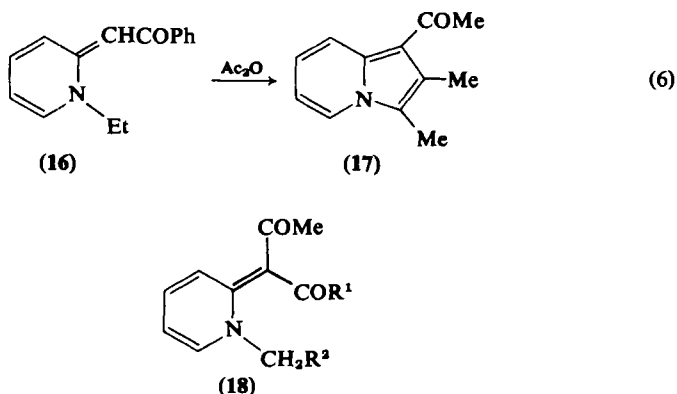
TABLE I

YIELDS FROM THE ACID ANHYDRIDE-CATALYZED CYCLIZATIONS OF SCHEME 4

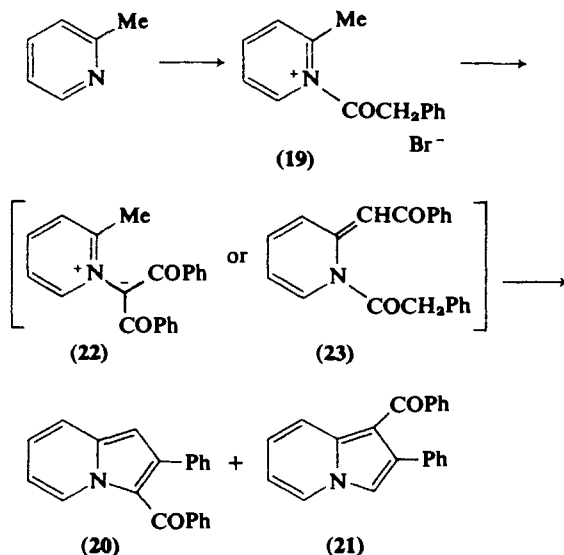
R	R ¹	R ²	Reaction time (hr)	% Yield		Method
				13a	13b	
Ph	Ph	Me	1	87	—	A
Ph	<i>p</i> NO ₂ C ₆ H ₄	Me	1	93	—	A
Ph	<i>p</i> MeOC ₆ H ₄	Me	1	27	—	A
Ph	Me	Me	12	9	—	A
OEt ^a	Ph	Me	2	83	—	A
Me	Ph	Me	1	90	—	A
Ph	PhCO	Me	1	—	—	A
H	Ph	Me	$\frac{1}{2}$	44	—	B
H	<i>p</i> ClC ₆ H ₄	Me	$\frac{1}{2}$	77	—	B
H	<i>p</i> MeOC ₆ H ₄	Me	$\frac{1}{2}$	32	—	B
H	<i>p</i> NO ₂ C ₆ H ₄	Me	$\frac{1}{2}$	68	31	B
H	<i>p</i> ClC ₆ H ₄	Ph	1	65	Trace	B
H	<i>p</i> NO ₂ C ₆ H ₄	Ph	1	25	42	B

^a The product is a 2-acetoxyindolizine.

ley³¹ and Kröck and Kröhnke⁴³ have shown that these reactions often proceed via a diacyl intermediate such as **18**.



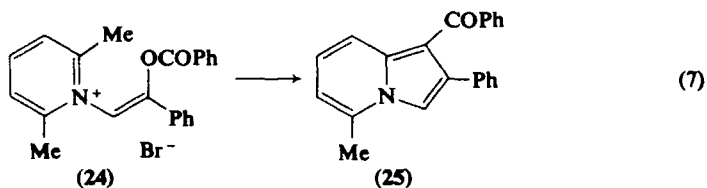
When a highly activated methylene group is present [e.g., in the conversion of 1-phenacyl-2-picolinium bromide (**19**) into a mixture of 3-benzoyl-2-phenylindolizine (**20**) and 1-benzoyl-2-phenylindolizine (**21**) using benzoic anhydride and triethylamine] the reaction could proceed through either of two intermediates, **22** or **23** (Scheme 5). Melton and



SCHEME 5

Wibberley formulated as **23** the intermediate they isolated from the treatment of the phenacyl quaternary salt with benzoyl chloride on the grounds that both **20** and **21** were formed when it was treated with acetic anhydride. However, Kröck and Kröhnke prepared the same intermediate by treating the quaternary salt of 2-picoline and dibenzoylmethyl bromide with potassium carbonate thus establishing its structure as **22**, and this was confirmed by infrared and NMR spectroscopy.

This same enol betaine was obtained by Flitsch and Gerstmann,⁴⁶ who also found that benzoylation of the quaternary salt of 2,6-lutidine with phenacyl bromide at room temperature gave the enol ester **24**. Benzoylation at elevated temperature or treatment of **24** with base gave the expected indolizine **25** [Eq. (7)].



⁴⁶ W. Flitsch and E. Gerstmann, *Chem. Ber.* **105**, 2344 (1972).

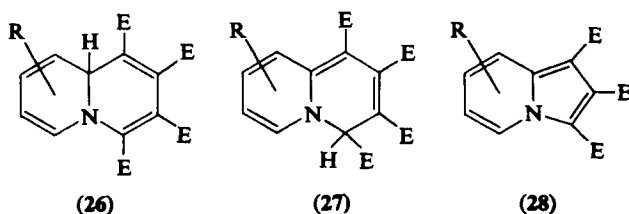
More recently, analogs of **20** and **21** have been prepared in a similar manner from 2,5-dimethyl-4-phenylpyridine and the same cyclization has also been effected using formamide instead of acetic anhydride.⁴⁷

C. CYCLOADDITION REACTIONS

1. "Nonpolar" Cycloadditions

The term "nonpolar" is used here to differentiate these reactions from those in the following section which involve dipolar cycloaddition and proceed by a completely different mechanism.

The reaction of pyridines and picolines with acetylenic compounds provides a useful synthesis of indolizines.⁴⁸ The reaction of such compounds with dimethyl acetylenedicarboxylate (DMAD), originally investigated by Diels and co-workers (see Ref. 4) has been reexamined more recently by several groups.⁴⁹⁻⁵² The two major adducts are now thought to be the quinolizines **26** and **27**, although Wiley and Knabeschuh⁵³ obtained the indolizine triester **28** when the reaction was carried out in ether as solvent. The adduct of type **27** is oxidized by nitric acid to **28**.



R = H or Me (E = COOMe throughout this section)

If pyridine and DMAD are allowed to react in cold methanol, a different indolizine is formed; originally formulated by Diels and

⁴⁷ N. S. Prostakov and O. B. Baktibaev, *Khim. Geterotsikl. Soedin.*, 788 (1974) [*CA* **81**, 120371 (1974)].

⁴⁸ G. Caronna and S. Palazzo, *Atti Accad. Sci. Lett. Arti Palermo, Parte I* **30**, 5 (1969-1970) [*CA* **77**, 151797 (1972)].

⁴⁹ E. van Tamelen, P. Aldrich, P. Bender, and D. Miller, *Proc. Chem. Soc.*, 309 (1959).

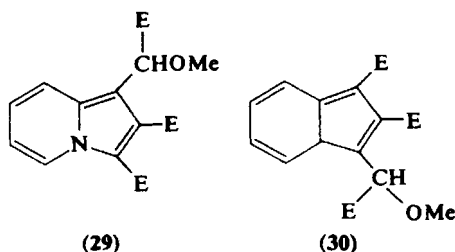
⁵⁰ L. M. Jackman, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 1579 (1960).

⁵¹ R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1691 (1960).

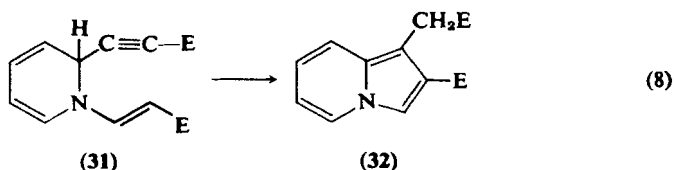
⁵² R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 4600 (1960).

⁵³ R. Wiley and L. Knabeschuh, *J. Org. Chem.* **18**, 836 (1953).

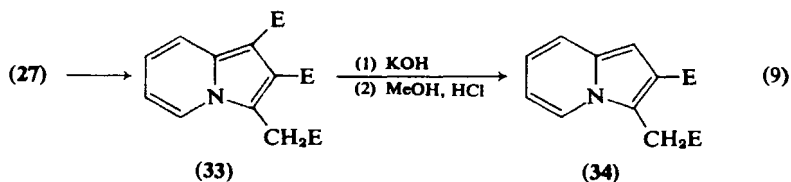
Meyer⁵⁴ as **29**, it was later shown to be **30**.⁵⁵ The course of this reaction is still uncertain.



Crabtree, Johnson, and Tebby⁵⁵ have studied the reaction of pyridine with methyl propiolate and found that the major product is **31**, high-pressure hydrogenation of which resulted in loss of the acrylic ester side chain to give indolizidin-3-one, whereas treatment with piperidine gave a product (**32**) believed to be the indolizine [Eq. (8)].



Attempts to confirm the structure of **32** by conversion into the methyl indolizine and comparison with an authentic sample were inconclusive. However, rearrangement of **27** with acetic acid or phenol gave an indolizine triester formulated as **33** which could be converted into **34**. This last product had markedly different physical properties from **32** and its decarboxylation product was identical with 3-methylindolizine [Eq. (9)].

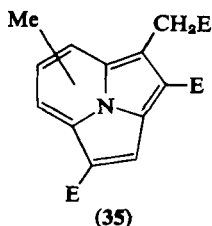


Acheson and Robinson also investigated the reaction of methyl propiolate with pyridine and its 3-methyl, 4-methyl, and 3,5-dimethyl

⁵⁴ O. Diels and R. Meyer, *Ann.* **513**, 129 (1934).

⁵⁵ A. Crabtree, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 3497 (1961).

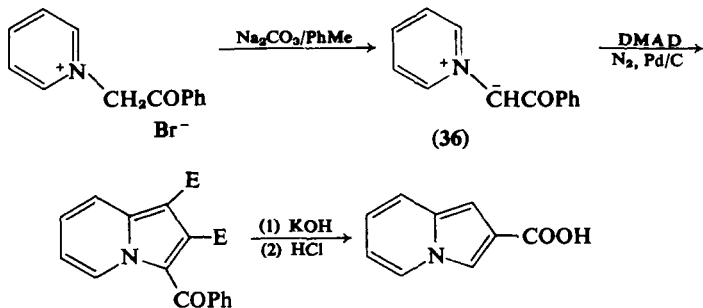
derivatives.⁵⁶ They were unable to obtain any of the dihydropyridine **31** but isolated instead **32** and also cyclazines of structure **35** in very low yield.



With a 2-substituent on the pyridine ring, the reaction becomes more straightforward.⁵⁷

2. Dipolar Cycloadditions

The substrate in this class of reaction⁵⁸⁻⁶⁰ (Scheme 6) is a pyridinium ylid, which undergoes a 1,3-cycloaddition with an acetylene. Sasaki and



SCHEME 6

his associates⁶¹ have studied the orientation of such cycloadditions to various heterocyclic nitrogen ylids. They showed by NMR analysis that 3-methyl- and 3-cyanopyridinium ylids gave mixtures of 6- and 8-

⁵⁶ R. M. Acheson and D. A. Robinson, *J. Chem. Soc. C*, 1633 (1968).

⁵⁷ R. M. Acheson and J. N. Bridson, *J. Chem. Soc. C*, 1143, (1969).

⁵⁸ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **44**, 803 (1971) [*CA* **75**, 5599 (1971)].

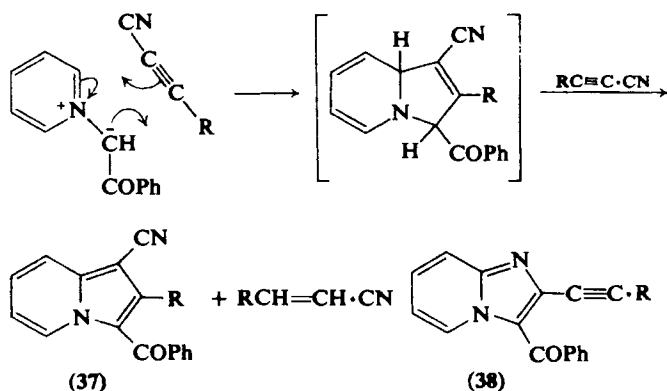
⁵⁹ C. A. Hendrick, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.* **20**, 2467 (1967).

⁶⁰ V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.* **83**, 458 (1961).

⁶¹ T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.* **36**, 813 (1971).

substituted indolizines with the latter predominating. No explanation was offered.

Cyanoacetylenes react in much the same way.⁶² Thus **36** with $\text{HC}\equiv\text{C}-\text{CN}$ or $\text{ClC}\equiv\text{C}-\text{CN}$ gives **37** ($\text{R} = \text{H}$ or Cl). A suggested mechanism is shown in Scheme 7. The formation of cyano-olefin by-products in each case supports the proposed aromatization step.



SCHEME 7

Spectroscopic evidence precludes structure **38** which would result from the alternative cycloaddition across the $\text{C}\equiv\text{N}$ bond.

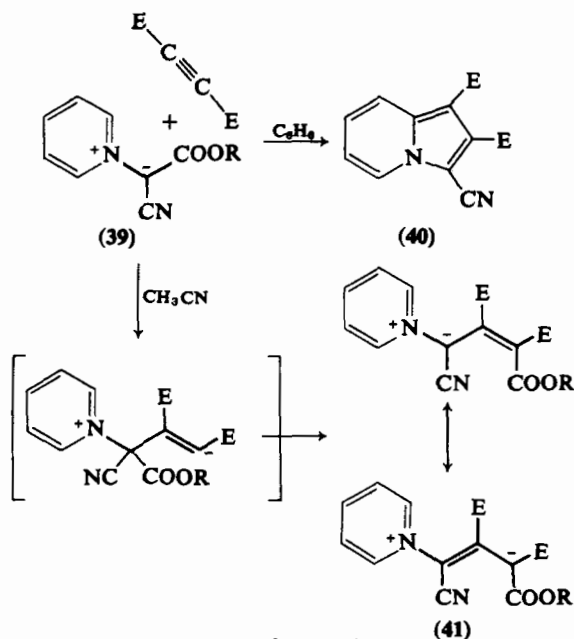
Recently, the reaction of DMAD with pyridinium arylsulfonyl methylides has been used as a simple route to indolizines.⁶³ The intermediate dihydroindolizines are readily aromatized by 1,4-elimination of *p*-toluenesulfinic acid.

The reaction of DMAD with the cyanocarboxy pyridinium methylide **39** in various solvents has also been studied.⁶⁴ In benzene the expected indolizine **40** was obtained. In dimethylformamide, the carboxy methylide gave some elimination of CN instead of COOR . However, in acetonitrile no indolizine was formed at all. The 1:1 crystalline adducts that were isolated were formulated on the basis of chemical and spectroscopic evidence as the highly stabilized ylids (**41**), formed by an internal rearrangement (Scheme 8).

⁶² T. Sasaki and K. Kanematsu, *J. Chem. Soc. C*, 481 (1970).

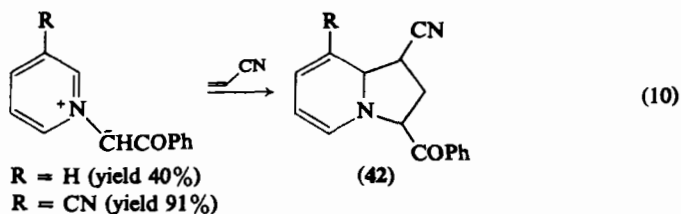
⁶³ R. A. Abramovitch and V. Alexanian, *J. Org. Chem.* **41**, 2144 (1976).

⁶⁴ C. Leonte and I. Zugravescu, *Tetrahedron Lett.*, 2029 (1972).



SCHEME 8

Acrylonitrile has been used instead of an acetylene for dipolar cyclo-additions, whereupon tetrahydroindolizines **42** are formed in reasonable yields [Eq. (10)].⁶⁵



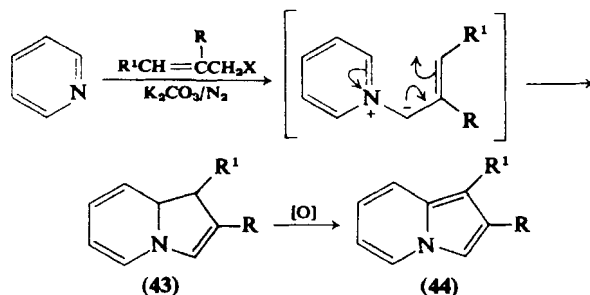
These products (**42**) may be dehydrogenated using palladium on charcoal as catalyst. In some cases, the 2,3-dihydro intermediates have been isolated. Analogous products are formed from quaternary salts of quinoline and isoquinoline.

Esters of various substituted acrylic acids have also been used, giving, on reaction with pyridinium methoxycarbonyl methylides, various 2,3-dihydroindolizine-1,3-dicarboxylates. These were stable and not

⁶⁵ J. Fröhlich and F. Kröhnke, *Chem. Ber.* **104**, 1621 (1971).

aromatized by heating but could be converted into indolizines with lead tetraacetate.⁶⁶

If an allyl halide is used as the quaternizing agent, an intramolecular 1,5-cyclization of the ylid may take place. In this way, various dihydro-indolizines, which are prone to oxidation and thus difficult to prepare, have been made.⁶⁷ The probable mechanism is shown in Scheme 9.



SCHEME 9

If R is benzoyl or acetyl and R¹ is phenyl, a dihydro product (43) is formed in over 90% yield. If R is H or phenyl, an indolizine (44) is the major product, and the ease of oxidation of 43 appears to depend on the nature of R¹. For an electron-donating group such as *p*-anisyl, the oxidation occurs very rapidly.

The 1,5-cyclization of ylids has been applied to the synthesis of several bridgehead N systems, including indolizines, by Japanese workers, notably Tamura's group.⁶⁸⁻⁷¹ Thus 45a-c on treatment with potassium carbonate in ethanol gave an indolizine 46 in high yield: no dihydro intermediate was isolated (Scheme 10).^{68,69}

However, 45d gave only 47 in 12% yield.⁷⁰ From these reactions and those shown in Scheme 11, this type of reaction appears to be somewhat unpredictable.^{71,72} Thus, whereas 48 and 52 gave the expected products (49 and 53), with the 2-picoline analog (50), cyclization to 51 took a

⁶⁶ A. Kahedi and S. Ito, *Bull. Chem. Soc. Jpn.* **47**, 938 (1974) [*CA* **81**, 25517 (1974)].

⁶⁷ E. Pohjala, *Tetrahedron Lett.*, 2585 (1972).

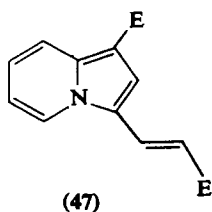
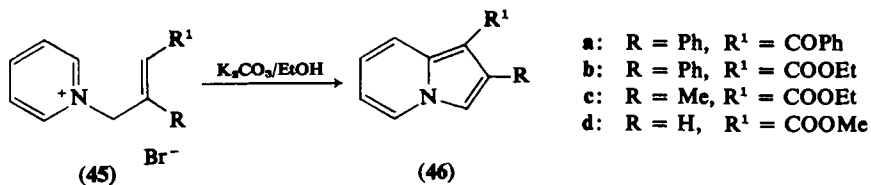
⁶⁸ Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron* **28**, 21 (1972).

⁶⁹ Y. Tamura, Y. Sumida, S. Tamada, and M. Ikeda, *Chem. Pharm. Bull.* **21**, 1139 (1973).

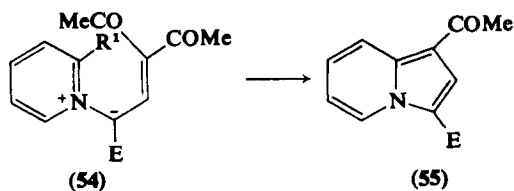
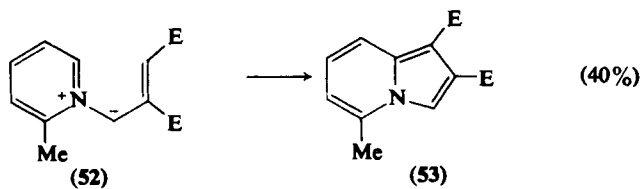
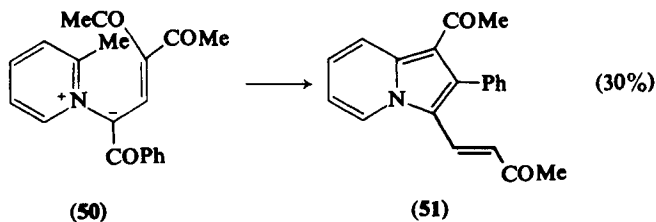
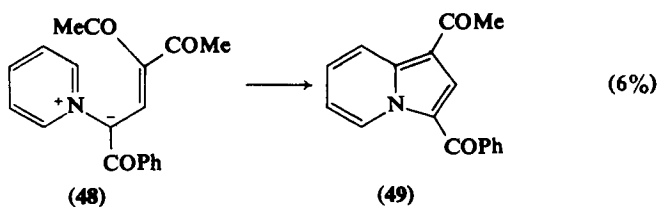
⁷⁰ Y. Tamura, Y. Sumida, and M. Ikeda, *Chem. Pharm. Bull.* **20**, 1058 (1972).

⁷¹ Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2091 (1973).

⁷² T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2089 (1973).



SCHEME 10



R¹ = H (yield 3%)
 R¹ = Me (yield 50%)

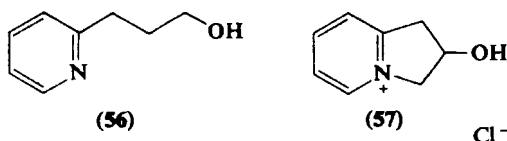
SCHEME 11

different course in which the methyl substituent was involved. Also, unexpectedly it was the picoline ylid (**54**) which gave the higher yield of indolizine (**55**). Tamura *et al.* suggest mechanisms to explain these results.⁷³

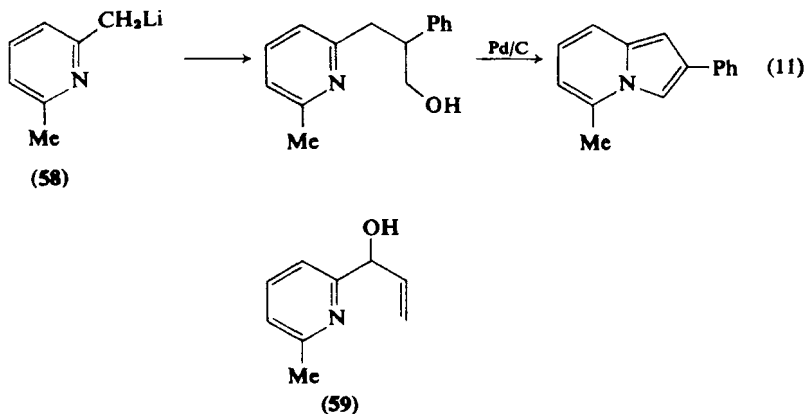
D. RING CLOSURE AT THE 3,4-POSITIONS

This route has been particularly investigated to provide indolizines unsubstituted in the five-membered ring, for which the Tschitschibabin reaction fails.

Indolizine itself has been synthesized in a one-step cyclization of 3-(2-pyridyl)propanol (**56**) in the presence of a dehydrogenation catalyst.⁴⁰ The yield was 55%. A second route involves the reaction of 2-pyridyllithium with epichlorohydrin to give **57**, which with base gives indolizine in 41% overall yield.⁷⁴



An analogous sequence [Eq. (11)] commences with the reaction of **58** with styrene oxide.⁴⁰

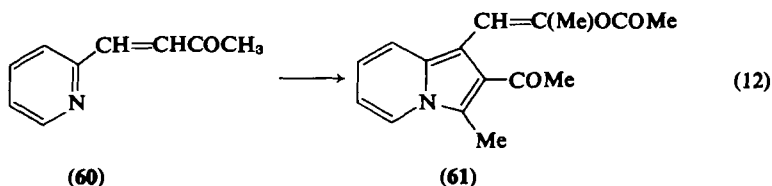


⁷³ Y. Tamura, Y. Sumida, S. Haruki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 575 (1975).

⁷⁴ W. Flitsch and E. Gerstmann, *Chem. Ber.* **102**, 1309 (1969).

A 30% yield of 5-methylindolizine has been obtained by the pyrolysis of the acetate of the carbinol **59** obtained by a Grignard reaction on 6-methylpyridine-2-carboxaldehyde.⁴⁰

Various indolizines are among the products reported by Pohjala in a series of papers devoted largely to the reactions of pyridine-2-carboxaldehyde.⁷⁵⁻⁷⁸ Under the conditions for the Perkin reaction (heating with acetic anhydride and potassium acetate) the expected pyridine acrylic acid is not isolated, instead 3-acetyl- and 3-acetoxyindolizines are produced among other products. In the presence of various methylene ketones, a wide variety of acylated indolizines was obtained by cyclizations of the aldols formed initially. In the most recent paper, high yields of indolizines are claimed from various 3-(2-pyridyl)-2-propen-1-ones.⁷⁸ Thus, 4-(2-pyridyl)-3-buten-2-one (**60**) on heating with potassium acetate in refluxing acetic anhydride gave 63% 1-(2-acetyl-3-methyl-1-indoliziny)-2-propenyl acetate (**61**) [Eq. (12)].



Scheme 12 shows a series of reactions between 2-bromomethylpyridine and compounds containing active methylene groups: the sequence 12(a) may be varied by using derivatives of acetylacetone or malonic ester instead of a β -ketoester.⁴⁰ Reactions 12(b) and 12(c) provide useful routes to 3-hydroxy and 3-amino compounds, which are noted for their instability in air (although **62** was stable in air for several weeks).³⁰

If 2-acylpyridine (**63**) is heated with a *p*-substituted benzaldehyde in the presence of acetic acid and ammonium acetate, an indolizine is produced⁷⁹ (Scheme 13). The first stage appears to be a normal aldol-type condensation followed by dehydration to give the substituted cinnamoylpyridine (**64**), which can be isolated if the reaction is carried out in an alkaline medium. The next step is presumably cyclization to

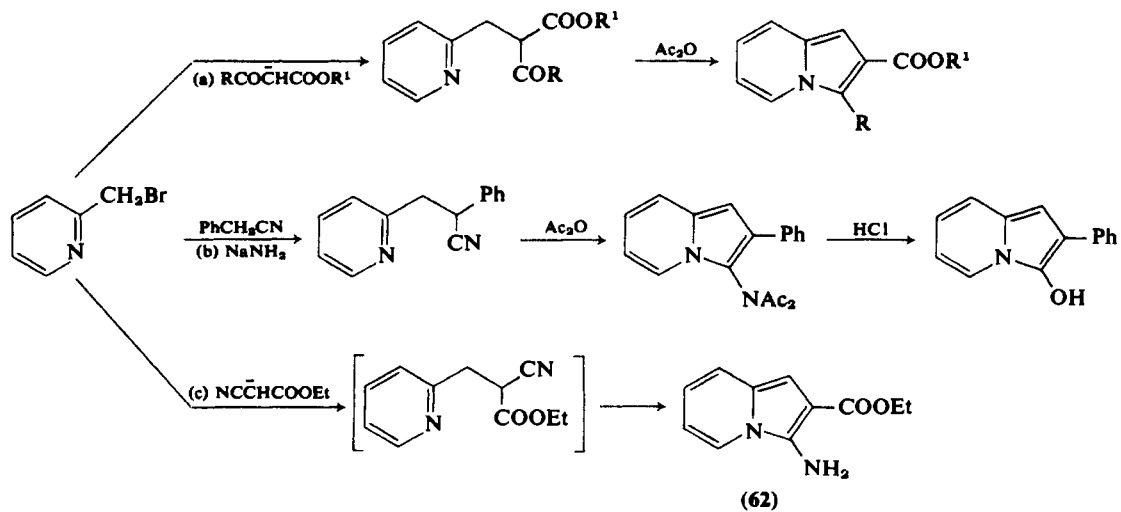
⁷⁶ E. Pohjala, *Acta Chem. Scand., Ser. B* **29**, 1079 (1975).

⁷⁸ E. Pohjala, *Heterocycles* **3**, 615 (1975).

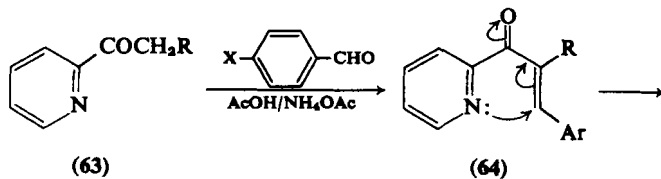
⁷⁷ E. Pohjala, *Acta Chem. Scand., Ser. B* **30**, 198 (1976).

⁷⁸ E. Pohjala, *Acta Chem. Scand., Ser. B* **30**, 512 (1976).

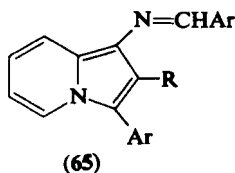
⁷⁹ F. W. Kröck and F. Kröhnke, *Chem. Ber.* **104**, 1629 (1971).



SCHEME 12

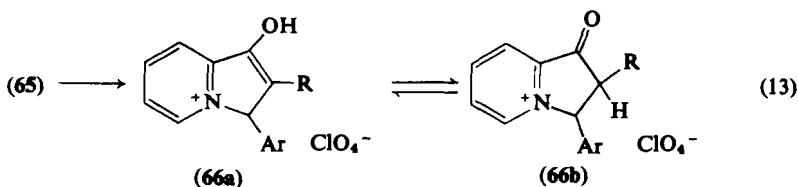


R = H, Me, or Ph
X = Cl, OMe, or NO₂

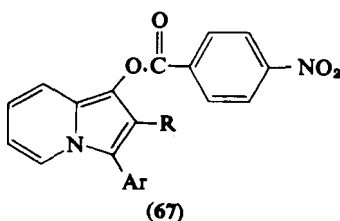


SCHEME 13

give a hydroxyindolizine, which reacts further to give an azomethine indolizine (65). Perchloric acid hydrolysis of this compound gives perchlorate salts (66) of hydroxyindolizines [Eq. (13)].

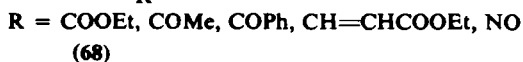
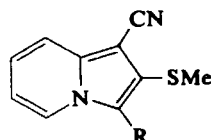


The position of the equilibrium of Eq. (13) depends markedly on the nature of R. When R = H the product is entirely the ketone, whereas when R = CH₃ the product can be shown from IR and NMR spectroscopic data to be completely enolized. Whichever form predominates, Schotten-Baumann benzoylation gives the indolizine *p*-nitrobenzoate ester (67). Acetic anhydride instead of perchloric acid with 65 gives the 1-acetamidoindolizine which is also available from the 1-acetyl compound via the Schmidt reaction.

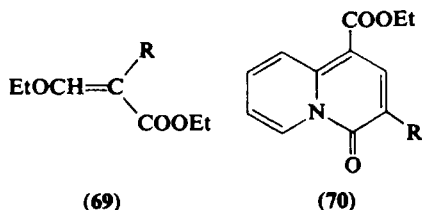


E. OTHER METHODS

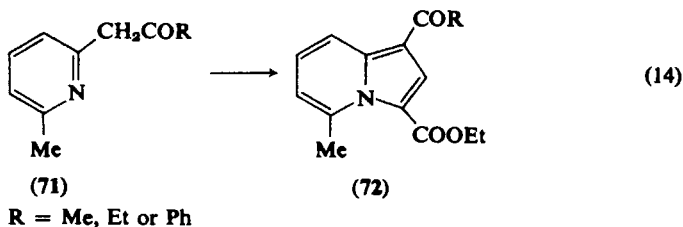
Various 3-substituted 1-cyano-2-methylthioindolizines (**68**) have been prepared by treating α -[bis(methylthio)methylene]-2-pyridine acetonitrile with α -haloketones and ethyl- γ -bromocrotonate; nitromethane gave the 3-nitroso compound.⁸⁰



Thyagarajan and Gopalakrishnan utilized the reaction of ethyl 2-pyridylacetate with reagents of the type **69**, where R = COOEt, NO₂, or COCH₃ to synthesize quinolizones of the general structure **70**.^{81,82} When they extended the reaction to some 2,6-lutidylketones (**71**), they found that, whereas quinolizones were formed when R = COOEt, an



indolizine (**72**) was the product when R = NO₂, presumably as a result of displacement of nitrite ion [Eq. (14)].⁸³



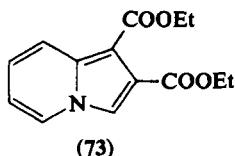
⁸⁰ C. Maseda, M. Sone, Y. Tominga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi* **94**, 839 (1974) [*CA* **81**, 152106 (1974)].

⁸¹ B. Thyagarajan and P. Gopalakrishnan, *Tetrahedron* **20**, 1051 (1964).

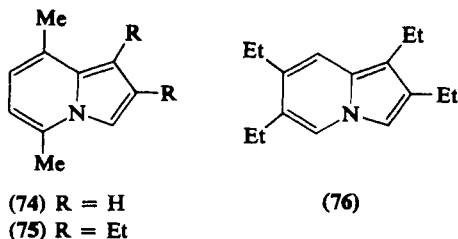
⁸² B. Thyagarajan and P. Gopalakrishnan, *Tetrahedron* **21**, 945 (1965).

⁸³ B. Thyagarajan and P. Gopalakrishnan, *Tetrahedron* **21**, 3305 (1965).

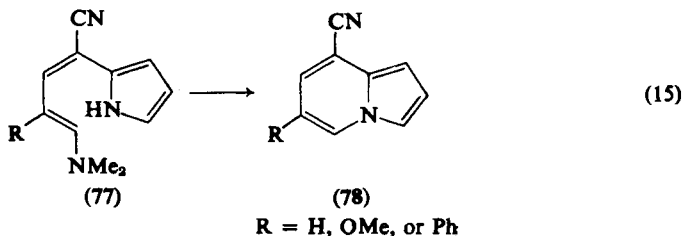
The reaction of ethyl bromopyruvate with ethyl 2-pyridylacetate, originally thought⁸⁴ to yield a quinolizine, has been shown by Bragg and Wibberley^{12,85} and by Kappe⁸⁶ to give the indolizine (73).



There are a few examples of the formation of indolizines from pyrroles. Thus pyrrole condenses with acetylacetone in the presence of zinc acetate to give 5,8-dimethylindolizine (74) as the major product.^{87,88} 3,4-Diethylpyrrole similarly gives 75.⁸⁹ This same compound undergoes self-condensation in the presence of zinc acetate to give 76 in 24% yield.⁸⁹ In another example tetramethine compounds (77) obtained from



2-cyanomethylpyrrole have been cyclized to 8-cyanoindolizines (78) by heating under nitrogen at 200°C [Eq. (15)].⁹⁰



⁸⁴ K. Winterfeld and W. Erning, *Arch. Pharm. (Weinheim)* **4**, 220 (1965).

⁸⁵ D. R. Bragg and D. G. Wibberley, *J. Chem. Soc. C*, 2120 (1966).

⁸⁶ T. Kappe, *Monatsh. Chem.* **98**, 1858 (1967).

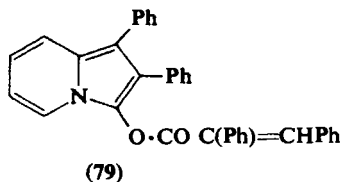
⁸⁷ L. K. Dalton and T. Teitei, *Aust. J. Chem.* **21**, 2053 (1968).

⁸⁸ C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).

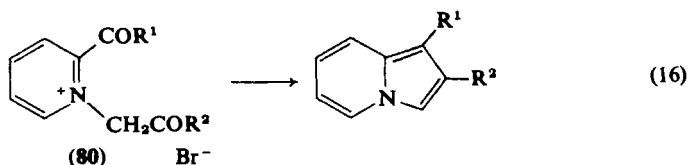
⁸⁹ R. Bonnett, I. Gale, and G. Stephenson, *J. Chem. Soc.*, 1518 (1965).

⁹⁰ C. Jutz, R. M. Wagner, and H. G. Loebering, *Angew. Chem.* **86**, 781 (1974).

Diphenylcyclopropenone has proved to be a useful synthetic reagent for preparing indolizines.⁹¹ It reacts readily with pyridine to give the indolizine **79** in 50% yield, and the yields of cyclized compounds tend to be greater when pyridazines and pyrazines are used instead of pyridines to give azaindolizines.



Indolizines are obtained in good yield when compounds of type **80** are treated with 25% hydrazine hydrate at room temperature⁹² [Eq. (16)]. The R¹ and R² may be methyl or aryl groups, but the yields are low if R² is not an aryl group.



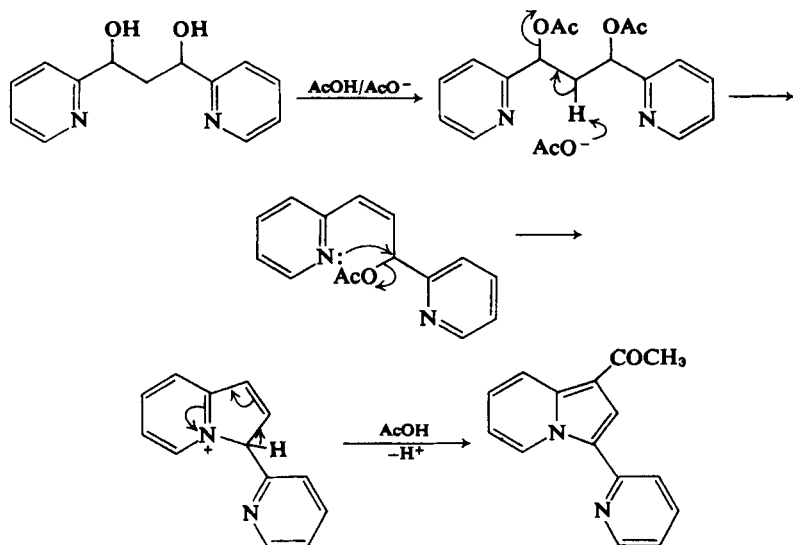
An interesting intramolecular cyclization takes place when 1,3-di-(2-pyridyl)-propane-1,3-diol is treated with sodium acetate in refluxing acetic acid.⁹³ 1-Acetyl-3-(2-pyridyl)indolizine is formed in 30% yield. Support for the proposed mechanism, shown in Scheme 14, is the observed increase in yield when the reaction is subjected to UV irradiation, which would be expected to increase the proportion of the *cis*-olefin present.

A new synthesis leading to a previously unknown 8-substituted indolizine involves initially the formation of the dihydropyridopyranyl ether (**81**) by reaction between a vinyl ether and a Mannich base obtained from 3-hydroxypyridine: treatment with dilute hydrochloric acid

⁹¹ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 1165 (1971).

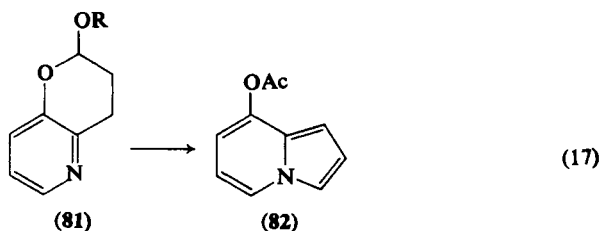
⁹² F. Kröhnke and W. Weis, *Ann.* **679**, 136 (1964).

⁹³ J. Michalski, K. Wojaczynski, and H. Zajac, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **9**, 401 (1961) [*CA* **60**, 6710 (1964)].



SCHEME 14

followed by heating with acetic anhydride and sodium acetate gives 8-acetoxyindolizine (82) via the hemiacetal [Eq. (17)].⁹⁴



III. Physical Properties of Indolizines

A. ELECTRONIC SPECTRA

Feitelson obtained good agreement between the ultraviolet spectrum of indolizine calculated from MO theory and the observed spectrum.⁹⁵ Mason studied the electronic spectra of indolizine and many of its

⁹⁴ H. Sliwa and D. Blondeau, *Tetrahedron Lett.*, 933 (1976).

⁹⁵ J. Feitelson, *J. Chem. Phys.* 43, 2511 (1965).

aza derivatives as well as analogous indoles.⁹⁶ The observed spectra could be satisfactorily explained using the indenyl anion as a model, indicating extensive π -electron delocalization in the indolizine system. Similar work has also been carried out by Evleth⁹⁷ and, more recently, by two groups of Italian workers.^{98,99} The fluorescence spectra of indolizines and aza analogs have been studied by Lerner and Evleth.^{100,101}

B. ACID-BASE PROPERTIES

The protonation of indolizines in acidic media has been shown by NMR studies to take place exclusively at the 3-position when unsubstituted.¹⁰²⁻¹⁰⁴ 3-Substituted compounds give mixtures of 1- and 3-protonated species depending on the nature and position of other substituents. Deuterium exchange also occurs preferentially in the 1- and 3-positions.¹⁰⁵⁻¹⁰⁷ It has also been reported recently that with 3-nitroso- and 3-phenylazo-2-alkyl indolizines, protonation occurs on the 3-substituent.¹⁰⁸

Armarego¹⁰⁹ has determined the pK_a values of indolizines and aza-indolizines from their ultraviolet spectra. He found that indolizine itself has the same basic strength as α -naphthylamine (pK_a 3.9) and that a methyl substituent increases the pK_a by two to three units. Mason and Smith,¹¹⁰ studying the fluorescence spectra of various aromatic nuclei including indolizine, found no evidence to support the prediction that acid-base properties of aromatic hydrocarbons in the first electronic excited state should differ from those in the ground state.

⁹⁶ S. F. Mason, *J. Chem. Soc.*, 3999 (1963).

⁹⁷ E. M. Evleth, *Theor. Chim. Acta* **16**, 22 (1970).

⁹⁸ V. Galasso, G. De Alti, and A. Bigotto, *Theor. Chim. Acta* **9**, 222 (1978).

⁹⁹ A. Gamba and G. Favini, *Gazz. Chim. Ital.* **98**, 167 (1968).

¹⁰⁰ D. A. Lerner and E. V. Evleth, *Chem. Phys. Lett.* **15**, 260 (1972).

¹⁰¹ D. A. Lerner, P. M. Horowitz, and E. M. Evleth, *J. Phys. Chem.* **81**, 12 (1977).

¹⁰² M. Fraser, A. Melera, B. B. Molloy, and D. H. Reid, *J. Chem. Soc.*, 3288 (1962).

¹⁰³ M. Fraser, S. McKenzie, and D. H. Reid, *J. Chem. Soc. B*, 44 (1966).

¹⁰⁴ W. L. F. Armarego, *J. Chem. Soc. B*, 191 (1966).

¹⁰⁵ W. Engewald, C. Weiss, and M. Mühlstädt, *Isotopenpraxis* **4**, 326 (1968).

¹⁰⁶ W. Engewald, C. Weiss, and M. Mühlstädt, *Tetrahedron* **27**, 851 (1971).

¹⁰⁷ W. Engewald, C. Weiss, and M. Mühlstädt, *Tetrahedron* **27**, 4171 (1971).

¹⁰⁸ M. Yu. Kornilov, G. P. Kutrov, and F. S. Babichev, *Ukr. Khim. Zh.* **41**, 1284 (1975) [*CA* **84**, 89021 (1976)].

¹⁰⁹ W. L. F. Armarego, *J. Chem. Soc.*, 4226 (1964).

¹¹⁰ S. F. Mason and B. E. Smith, *J. Chem. Soc. A*, 325 (1969).

C. THEORETICAL CALCULATIONS

The first ionization potential of indolizine has been calculated by the "omega" method as 7.27 eV.¹¹¹ The theoretical treatment of indolizine and similar ring systems has continued to be refined.¹¹²⁻¹¹⁶ An MO calculation gave the following order of charge density for indolizine:¹¹⁷ $4 \gg 3 > 1 \gg 5 > 2 > 7 > 6 > 8$, whereas the "frontier-electron-density" order has been calculated¹¹⁸ to be $3 > 1 \gg 5 > 8 > 7 > 6 > 8a > 4 > 2$. Calculations on 3-(*p*-dimethylaminobenzylidene)-2-phenylindolizine using free-electron molecular orbital theory (FEMO) have shown greater electrophilicity of position 3 over position 1 in 2-phenylindolizine.¹¹⁹

D. MASS SPECTRA

The mass spectra of indolizine and some of its alkyl derivatives have been observed and the fragmentation patterns compared with those of indoles.^{120,121}

E. INFRARED SPECTRA

There appears to have been no systematic study of the infrared spectra of indolizines. The general lack of significant IR information in papers dealing with organic heterocyclic chemistry published in recent years may be attributed to the greater usefulness of NMR data.

F. NMR SPECTRA

The proton NMR spectra of some indolizines have been analyzed in detail by Black and co-workers¹²² and the chemical shifts compared with those calculated from various theoretical approaches.¹²³⁻¹²⁵

¹¹¹ A. Streitwieser, *J. Am. Chem. Soc.* **82**, 4123 (1960).

¹¹² C. Aussems, S. Jaspers, G. Leroy, and F. van Remoortere, *Bull. Soc. Chim. Belg.* **78**, 479 (1969).

¹¹³ V. Galasso, *Gazz. Chim. Ital.* **99**, 1078 (1969).

¹¹⁴ M. J. S. Dewar and N. Trinajstić, *Theor. Chim. Acta* **17**, 235 (1970).

¹¹⁵ W. W. Paudler and J. S. Casman, *J. Heterocycl. Chem.* **10**, 499 (1973).

¹¹⁶ S. Becker, D. Heidrich, C. Weiss, and J. Pancir, *Z. Chem.* **14**, 440 (1974).

¹¹⁷ C. A. Coulson and H. C. Longuet-Higgins, *Trans. Faraday Soc.* **43**, 87 (1947).

¹¹⁸ K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

¹¹⁹ A. Sharma and G. B. Behera, *Indian J. Chem.* **13**, 977 (1976).

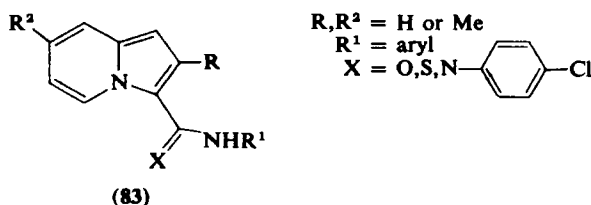
¹²⁰ G. Jones and J. Stanyer, *Org. Mass Spectrom.* **3**, 1489 (1970).

¹²¹ P. B. Terent'ev, S. M. Vinogradova, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 509 (1975) [*CA* **83**, 140719 (1975)].

¹²² P. J. Black, M. L. Heffernan, L. M. Jackman, Q. Porter, and G. Underwood, *Aust. J. Chem.* **17**, 128 (1964).

Some ^{13}C NMR spectra have been studied in a similar way,¹²⁶ whereas the ^{14}N NMR spectrum of indolizine has been recorded among those of a large number of other N-containing compounds.¹²⁷

A proton NMR study by Mirek and Bogdanowicz-Szwed¹²⁸ observed that the 5-proton was significantly deshielded in 3-amide, -thioamide, and -amidine derivatives, and this established the preferred conformation as **83**.



G. X-RAY DIFFRACTION

The crystal and molecular structure of 1-(2-pyridyl)-3-benzoyl-6-bromoindolizine has been obtained by the heavy atom method.¹²⁹ The larger than normal $\text{C}=\text{O}$ distance (1.32 Å compared with 1.22 Å for a carboxy group) suggests significant contributions from charged canonical forms.

IV. Reactions of Indolizines

A. SUBSTITUTION

The most widely investigated reaction of the indolizine nucleus has been electrophilic substitution. Molecular orbital calculations of varying degrees of sophistication show that the most reactive positions on the

¹²³ W. W. Paudler and J. E. Kuder, *J. Heterocycl. Chem.* **3**, 33 (1966).

¹²⁴ P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.* **20**, 1305, (1967).

¹²⁵ P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.* **20**, 1325 (1967).

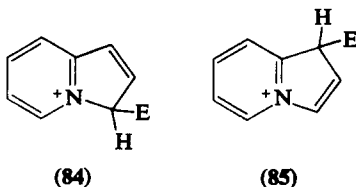
¹²⁶ D. M. Grant, R. J. Pugmire, M. J. Robins, and R. K. Robins, *J. Am. Chem. Soc.* **93**, 1887 (1971).

¹²⁷ D. Herbison-Evans and R. E. Richards, *Mol. Phys.* **8**, 19 (1964).

¹²⁸ J. Mirek and K. Bogdanowicz-Szwed, *Zesz. Nauk. Uniw. Jagiellon. Pr. Chem.*, 179 (1973) [*CA* **80**, 2723 (1974)].

¹²⁹ L. A. Aslanov, V. M. Ionov, I. S. Akhired Farag, V. A. Tafeenko, S. M. Vinogradova, A. N. Kost, and P. B. Terent'ev, *Zh. Strukt. Khim.* **17**, 746 (1976) [*CA* **86**, 10952 (1977)].

nucleus are 3 and 1, in that order. The Wheland intermediates, **84** and **85**, show that the aromaticity of the pyridine ring is retained in each case.



These theoretical predictions are supported by experimental evidence; virtually all the electrophilic substitution reactions that have been reported are at one or both of these positions.

In view of the diversity of these reactions, they will be subdivided according to the type of substituted indolizine produced.

1. Alkyl and Alkylidene Derivatives

The synthesis of these derivatives from the appropriate pyridine compound is usually more convenient than by alkylation of an indolizine, and almost any pattern of alkyl or alkylidene substitution can be achieved using the methods of synthesis already described.

The Mannich reaction has been used to good effect in indolizine chemistry, notably by Harrell and Doerge in the preparation of a large number of potential CNS depressants from phenylindolizines and a variety of secondary amines.¹³⁰⁻¹³⁶ 1,2-Diphenylindolizine reacted at the 3-position,¹³⁰⁻¹³² 2-phenyl-3-ethylindolizine at the 1-position,¹³³ and 2-phenylindolizine at the 1- and 3-positions.¹³⁴ The biological activity of these compounds has been reviewed¹³⁵ and their chromatographic behavior examined.¹³⁶

Some indolizine-1-acetic acids (**87**) have also been prepared^{137,138} by using the Mannich reaction, and these were found to exhibit analgesic activity. After initial aroylation, reaction with dimethylamine and

¹³⁰ W. B. Harrell and R. F. Doerge, *J. Pharm. Sci.* **56**, 1200 (1967).

¹³¹ W. B. Harrell, *J. Pharm. Sci.* **59**, 275 (1970).

¹³² W. B. Harrell, S. Kuang, and C. O'Dell, *J. Pharm. Sci.* **59**, 721 (1970).

¹³³ W. B. Harrell and R. F. Doerge, *J. Pharm. Sci.* **56**, 225 (1967).

¹³⁴ W. B. Harrell and R. F. Doerge, *J. Pharm. Sci.* **57**, 1989 (1968).

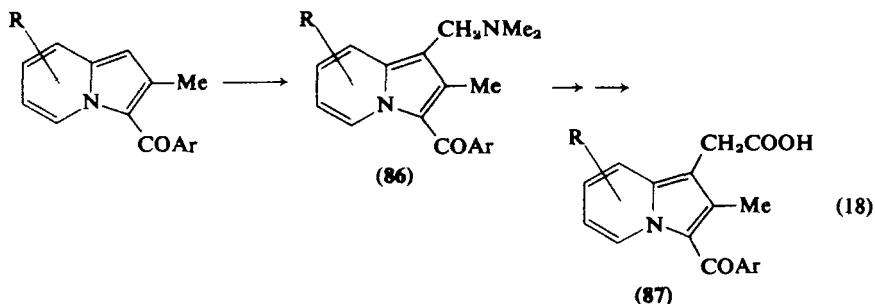
¹³⁵ W. B. Harrell, *Diss. Abstr.* **B 27** (11), 3876 (1967).

¹³⁶ N. H. Choulis and W. B. Harrell, *J. Pharm. Sci.* **60**, 486 (1971).

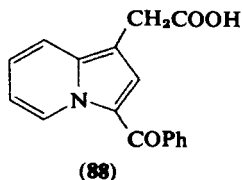
¹³⁷ J. H. C. Nayler, British Patent 1,174,124 (1969) [*CA* **72**, 55285 (1970)].

¹³⁸ A. G. Brown and J. H. C. Nayler, *Ger. Offen.* 2,046,904 (1971) [*CA* **75**, 48933 (1971)].

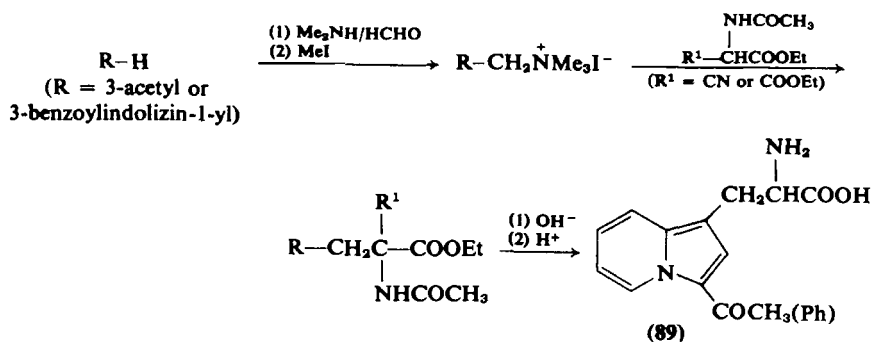
formaldehyde in the presence of acetic anhydride gave the tertiary amine **86**. Quaternization with methyl iodide followed by reaction with potassium cyanide gave the corresponding cyanide, which was converted into the acid (**87**) by base hydrolysis and acidification, as shown in Eq. (18).



A shorter method has been used to prepare indolizine-1-acetic acid (**88**) by reaction with diazoacetic ester followed by base hydrolysis and acidification.¹³⁹



Two groups of workers^{139,140} have independently synthesized indolizin-1-ylalanine (**89**) along similar lines (Scheme 15).

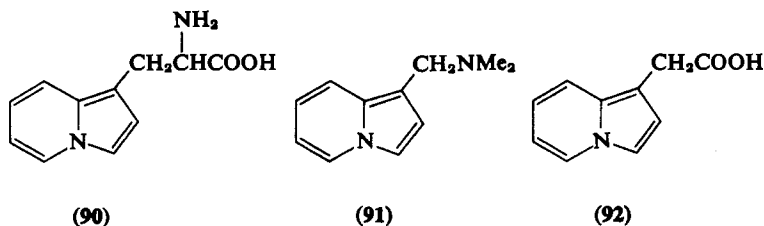


SCHEME 15

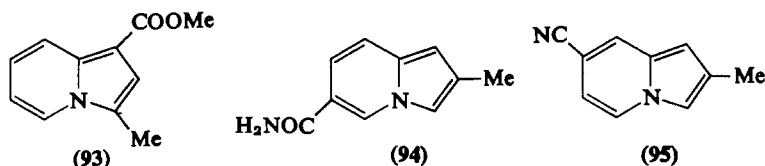
¹³⁹ M. Cardellini, S. Ottolino, and P. Tafaro, *Ann. Chim. (Rome)* **58**, 1206 (1968).

¹⁴⁰ J. A. Carbon and S. Brehm, *J. Org. Chem.* **26**, 3376 (1961).

Some indolizines (90–92) have been prepared because of their structural similarity to naturally occurring indoles: tryptophan, gramine, and heterauxin, respectively.



Ames and co-workers have reported the synthesis of some aminoethyl indolizines.¹⁴¹ Workers at Keele University have investigated the preparation of hydroxymethyl and aminomethyl derivatives.¹⁴² They obtained the 2-, 3-, and 6-hydroxymethyl compounds by lithium aluminum hydride (LAH) reduction of the esters. However, compound 93 gave inseparable mixtures on reduction, and whereas the 2-aminoethyl compound could be made by reduction of the corresponding



amide, attempted LAH reduction of 94 resulted in partial reduction of the pyridine ring, presumably due to activation of the 5-position by the adjacent electron-withdrawing group. By contrast, the 7-cyano compound (95) was reduced smoothly to the aminomethyl derivative. Melton and Wibberley³¹ reduced 1-cyanoindolizine, but the aminomethyl product obtained was rather unstable. Some 2-aminoethyl derivatives have been synthesized as potential oral hypoglycemic agents by straightforward routes.^{143,144}

2-Phenylindolizine undergoes Michael-type addition reactions with 2- and 4-vinylpyridine and with acrylophenone to form 96 and 97,

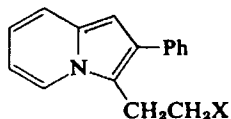
¹⁴¹ D. E. Ames, T. F. Grey, and W. A. Jones, *J. Chem. Soc.*, 620 (1959).

¹⁴² G. Jones and J. Stanyer, *J. Chem. Soc. C*, 901 (1969).

¹⁴³ A. U. De and B. P. Saha, *J. Pharm. Sci.* **62**, 1897 (1973).

¹⁴⁴ A. U. De and B. P. Saha, *J. Pharm. Sci.* **64**, 249 (1975).

respectively.¹⁴⁵ Similar reactions with other activated olefins, such as acrylate esters or acrylonitrile, can be expected.

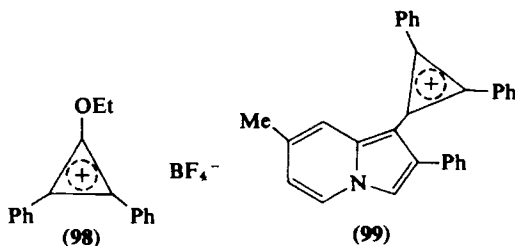


(96) X = 2- or 4-pyridyl

(97) X = CPh

Indolizines also react readily with activated halides such as picryl chloride¹⁴⁶ and tricyanovinyl chloride¹⁴⁷ to form highly colored derivatives.

A somewhat unusual "alkylation," which may be included here for convenience, is the reaction of diphenylcyclopropenone¹⁴⁸ or the salt **98**¹⁴⁹ with an indolizine to form the cation **99**, isolated as its tetrafluoroborate salt.



Over the years, the indolizine nucleus has been incorporated into many mono- and polymethine dyes, some of which have found application in photographic work.¹⁵⁰⁻¹⁵⁴ Reactions of 1,2-dimethylindolizine with $(\text{EtO})_2\text{CHCH}=\text{CHOEt}$ and acetic anhydride in the presence of potassium bromide gave a trimethine dye (**100**).

¹⁴⁵ L. Pentimalli and S. Bozzini, *Ann. Chim. (Rome)* **56**, 752 (1966).

¹⁴⁶ W. Treibs and W. Wahren, *Chem. Ber.* **94**, 2142 (1961).

¹⁴⁷ J. R. Roland and B. C. McKurick, *J. Am. Chem. Soc.* **83**, 1652 (1961).

¹⁴⁸ J. H. M. Hill and M. A. Battiste, *Tetrahedron Lett.*, 5537 (1968).

¹⁴⁹ T. Eicher and A. Hansen, *Tetrahedron Lett.*, 4321 (1967).

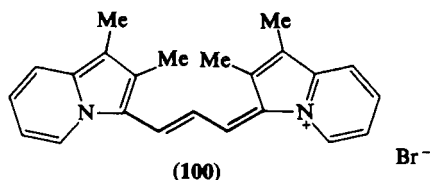
¹⁵⁰ F. N. Stepanov and L. I. Lukashina, *Zh. Obshch. Khim.* **30**, 2850 (1960) [*CA* **55**, 15481 (1961)].

¹⁵¹ J. Bailey, Belgian Patent 649,903 (1964) [*CA* **64**, 11358 (1966)].

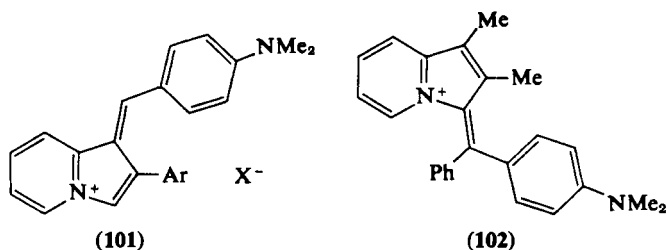
¹⁵² J. Bailey, *Ind. Chim. Belge* **32**, 90 (1967).

¹⁵³ F. N. Stepanov and L. I. Lukashina, *Zh. Obshch. Khim.* **33**, 2364 (1963) [*CA* **60**, 695 (1964)].

¹⁵⁴ J. Bailey, British Patent 999,874 (1965) [*CA* **63**, 16511 (1965)].



The reaction has been applied to 5,6,7,8-tetrahydroindolizines^{151,152}; the length of the methine chain and the position of attachment to the rings have been varied, and a different heterocyclic system used for the second nucleus.^{151,153,155} Other types of dyes, e.g., **101** and **102**, were produced by reaction of indolizines with aromatic aldehydes or ketones.¹⁵⁶⁻¹⁵⁸



2. Acyl and Thioacyl Derivatives

Carboxylic acid derivatives, as well as aldehydes and ketones, together with the corresponding sulfur compounds, have been included in this section. The reactivity of the 1- and 3-positions is such that in syntheses using acetic anhydride it is often impossible to prevent acetylation. Acyl derivatives may be formed from acid chlorides,^{44,159-161} cyclobutenedione derivatives,¹⁶² or esters.¹⁶³ Thus, reaction of a substituted in-

¹⁵⁵ R. A. Jeffreys and E. A. Gloag, Ger. Offen. 2,117,087 (1971) [CA 76, 60969 (1972)].

¹⁵⁶ E. A. Kochetkova, Sb. Nauchn. Tr. Vladimir. Vech. Politekh. Inst., 146 (1969) [CA 74, 88647 (1971)].

¹⁵⁷ F. N. Stepanov and N. A. Aldanova, Khim. Tekhnol. Promenerie Proizvodnykh Piridina Khinolina, Materialy Soveshchaniya, Inst. Khim., Akad. Nauk. Latv. SSR Riga, 203 (1957) [CA 55, 23529 (1961)].

¹⁵⁸ G. Yu. Turchinovich, Tr. Kiev. Politekh. Inst. 43, 81 (1963) [CA 62, 10559 (1965)].

¹⁵⁹ V. S. Venturella, J. Pharm. Sci. 53, 107 (1964).

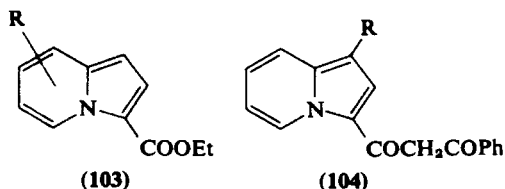
¹⁶⁰ V. S. Venturella, J. Pharm. Sci. 53, 1166 (1964).

¹⁶¹ G. Rosseals, H. Inion, J. R. Matteazzi, M. Peiren, M. Prost, M. Deschamps, C. Tornay, M. Colot, and R. Charlier, Eur. J. Med. Chem.—Chim. Ther. 10, 579 (1975) [CA 84, 150535 (1976)].

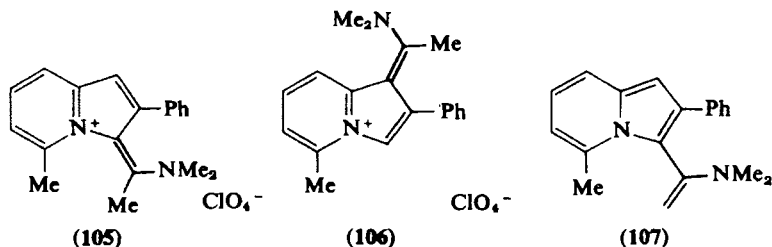
¹⁶² W. Ried and H. Medem, Synthesis 9, 670 (1974).

¹⁶³ F. N. Stepanov and N. I. Grineva, Zh. Obshch. Khim. 32, 1529 (1962) [CA 59, 4499 (1963)].

dolizine with ethyl chloroformate and ethyl benzoylacetate gave **103** and **104**, respectively. Conversely, acyl groups in these positions are readily removed with mineral acid.⁴ Sodium borohydride has also been used.¹⁸⁴



The Vilsmeier reaction has been applied to indolizines to yield a variety of products. The normal reaction conditions with *N,N*-dimethylformamide and phosphorus oxychloride can give the indolizine-1-aldehyde,¹⁵⁸ e.g., with 6-ethyl-2,3-dimethylindolizine. However, *N,N*-dimethylacetamide with 5-methyl-2-phenylindolizine gave a mixture of isomers, **105** and **106**, with the former predominating.¹⁶⁵ Hydrolysis of **105** gave enamine **107** instead of the acetyl compound.



The reaction of indolizine with *N,N*-dimethylformamide and phosphorus oxychloride gave almost exclusively indolizine-3-aldehyde.¹⁶⁶ The Vilsmeier formylation of 6-ethoxycarbonyl-2-methylindolizine gave the 1,3-dialdehyde, but with the corresponding 2-phenyl compound the product was almost totally the 3-aldehyde.¹⁶⁷

McKenzie and Reid have prepared several thioaldehyde derivatives (**108**) by solvolysis of the intermediate Vilsmeier salts with sodium

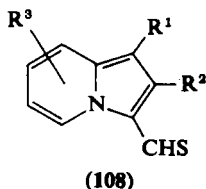
¹⁸⁴ I. Dainis, *Aust. J. Chem.* **25**, 2013 (1972).

¹⁸⁵ W. K. Gibson and D. Leaver, *J. Chem. Soc. C*, 324 (1966).

¹⁸⁶ O. Fuentes and W. W. Paudler, *J. Heterocycl. Chem.* **12**, 379 (1975).

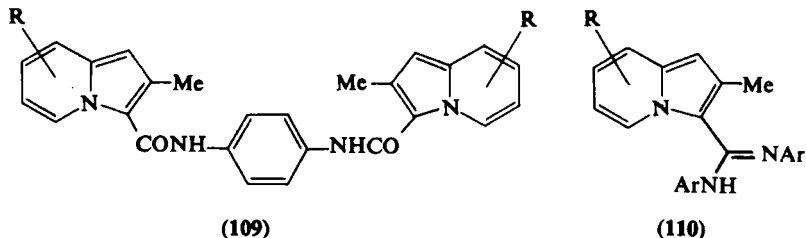
¹⁸⁷ T. S. Loseva, A. D. Yanina, E. E. Mikhlin, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 209 (1976) [*CA* **85**, 21063 (1976)].

hydrogen sulfide.^{168,169} From 2-substituted indolizines, the 3-thioformyl compound was almost always the exclusive product.



A preliminary electrochemical investigation of 1,2-dimethyl-3-thioformylindolizine in acetonitrile using mercury electrodes indicated that an initial quasi-reversible electrochemical reduction was followed by an irreversible process with possible loss of hydrosulfide ion.¹⁷⁰

A large number of thioamide derivatives have been obtained by Mirek and associates by allowing substituted indolizines to react with an aryl^{171,172} or aroyl¹⁷³ isothiocyanate in a refluxing inert solvent. If a diisocyanate or a carbodiimide is used, products such as **109** and **110** are formed.¹⁷⁴



The isocyanate may be generated *in situ* via a Curtius rearrangement of an acyl azide.¹⁷⁵ Substitution has been observed to take place exclusively at the 3-position if unsubstituted. Hydrolysis of compounds

¹⁶⁸ S. McKenzie and D. H. Reid, *J. Chem. Soc., Chem. Commun.*, 401 (1966).

¹⁶⁹ S. McKenzie and D. H. Reid, *J. Chem. Soc. C*, 145 (1970).

¹⁷⁰ J. N. Cope and C. A. Vincent, *J. Electroanal. Chem. Interfacial Electrochem.* **56**, 427 (1974).

¹⁷¹ J. Mirek, *Rocz. Chem.* **41**, 307 (1967) [*CA* **67**, 73507 (1967)].

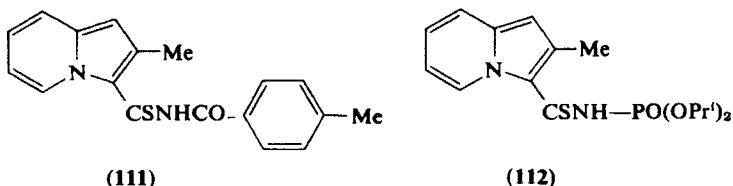
¹⁷² J. Mirek, B. Kawalek, and Z. Hojka, *Zesz. Nauk. Uniw. Jagiellon. Pr. Chem.*, 95 (1969) [*CA* **72**, 31580 (1970)].

¹⁷³ J. Mirek and J. Mazurek, *Rocz. Chem.* **42**, 79 (1968) [*CA* **69**, 24342 (1968)].

¹⁷⁴ K. Bogdanowicz-Szwed and B. Kawalek, *Zesz. Nauk. Uniw. Jagiellon., Pr. Chem.*, 187 (1973) [*CA* **80**, 47763 (1974)].

¹⁷⁵ J. Mirek, *Rocz. Chem.* **40**, 61 (1966) [*CA* **65**, 3821 (1966)].

such as **111** leads to the corresponding nitrile or primary amide.¹⁷⁶ Phosphorus derivatives such as **112** may be obtained by similar methods.¹⁷⁷



3. Halogen Derivatives

Very little work has been carried out on halogenated compounds.⁴ The preparation of iodo derivatives, discussed in a recent review,¹⁷⁸ appears to be very straightforward. Thus 1-acetyl-2-methylindolizine is converted into the 3-iodo compound by iodine and sodium acetate.²⁹

4. Nitro and Nitroso Derivatives

Nitration of indolizines is seldom attempted in view of accompanying oxidation reactions. Thus the synthesis of 6- and 8-nitro-2-phenylindolizine has been achieved by the cyclization of appropriately substituted 2-methyl-1-phenacylpyridinium bromide.¹⁷⁹ However, 1-nitro and 1,3-dinitro compounds have been prepared.⁴ From the behavior of the indolizine nucleus toward other electrophiles, 3-nitroindolizine might be expected to be the primary product. This compound has been synthesized using a dilute solution of nitric acid in acetic acid at -70°C where the substrate could well be the base and not the 3-protonated cation as in a nitric acid-sulfuric acid mixture.¹⁸⁰

A novel reaction of nitro-substituted 2,3-dihydroindolizines (**113**) was the claimed conversion into substituted indoles on refluxing with base in an organic solvent.¹⁸¹

¹⁷⁶ J. Mirek and J. Mazurek, *Rocz. Chem.* **44**, 2035 (1970) [*CA* **75**, 20129 (1971)].

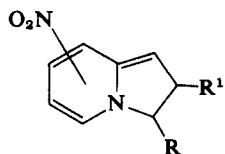
¹⁷⁷ P. Nguyen, Z. M. Ivanova, G. I. Derkack, and F. S. Babichev, *Zh. Obshch. Khim.* **41**, 319 (1971) [*CA* **75**, 48877 (1971)].

¹⁷⁸ W. Treibs, *Jerusalem Symp. Quantum Chem. Biochem.* **3**, 91 (1971).

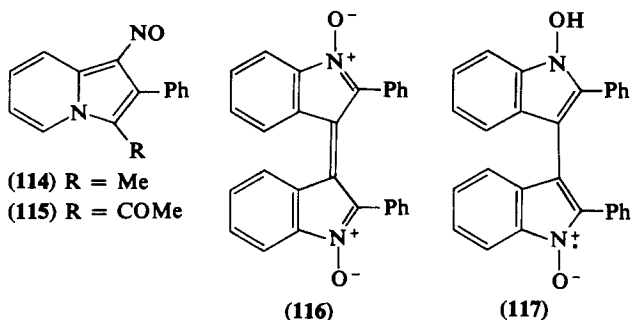
¹⁷⁹ A. N. Kost, R. S. Sagitullin, and S. P. Gromov, *Khim. Geterosikl. Soedin.*, 922 (1976) [*CA* **85**, 177183 (1976)].

¹⁸⁰ J. A. Hickman and D. G. Wibberley, *J. Chem. Soc., Perkin Trans. I*, 2954 (1972).

¹⁸¹ R. S. Sagitullin, S. P. Gromov, and A. N. Kost, *Otkrytiya. Izobret. Prom. Obrabztsy, Tovarnye Znaki* **53**, 55 (1976) [*CA* **85**, 159876 (1976)].

(113) R, R¹ = H, alkyl, aryl

Indolizines are readily nitrosated in the 1- or 3-position by the action of nitrous acid^{4,182} or *N*-nitrosodiphenylamine.¹⁸³ The nitroso derivatives **114** and **115** have been shown to oxidize 1-hydroxy-2-phenylin-



dole¹⁸⁴ to **116** and **117** and others to effect the oxidative cleavage of 3-aminoindolizines¹⁸⁵ (see Section IV,A,5).

5. Amino and Azo Derivatives

Simple aminoindolizines have been found to be rather unstable to light and air^{30,31} and, until recently, very few had been isolated in the pure state. However, workers at Aston University have succeeded in preparing eight new 3-aminoindolizines by various reductions of 3-nitro, 3-azo, or 3-nitroso precursors.¹⁸⁰ Catalytic hydrogenation was unsatisfactory, as ring cleavage occurred with the formation of products of the types **118** and **119**. In a study of the factors affecting such ring-cleavage reactions, Hickman and Wibberley found that both lead tetraacetate and triethylphosphite catalyzed the ring opening of nitroso and aminoindolizine.¹⁸⁵ They also found that 2-phenyl-3-aminoindolizine was converted into **121** in 71% yield by its 3-nitroso precursor

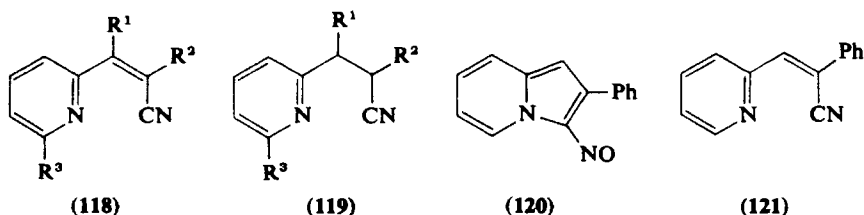
¹⁸² J. M. Tedder, K. H. Todd, and W. K. Gibson, *J. Chem. Soc. C*, 1279 (1969).

¹⁸³ M. Colonna and P. Bruni, *Gazz. Chim. Ital.* **95**, 857 (1965).

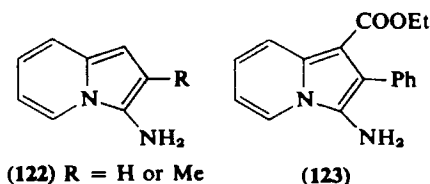
¹⁸⁴ M. Colonna, L. Greci, and G. Padovano, *Gazz. Chim. Ital.* **101**, 81 (1971).

¹⁸⁵ J. A. Hickman and D. G. Wibberley, *J. Chem. Soc., Perkin Trans. 1*, 2958 (1972).

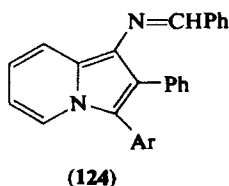
(120), thus helping to explain the appearance of unwanted products in the hydrogenations.



However, the use of hydrazine hydrate and a palladium catalyst for the reduction gave high yields of the amines. The crystalline amines all decomposed on exposure to air or hot solvents. The rates of decomposition varied; thus, compounds **122** were stable for up to 1 hr, whereas **123** was much more stable, only decomposing after several months.



Most of the amines could be acetylated at nitrogen and, under refluxing conditions, at the 1-position. Other routes to acetamidoindolizines are from the corresponding acetyl compounds via the Schmidt reaction,^{79,180} from pyridines via Tschitschibabin reactions, and from acetolysis of an azomethine⁷⁹ such as **124**, which may be derived from the reaction of an indolizine and diphenylformamidine.¹⁸⁶

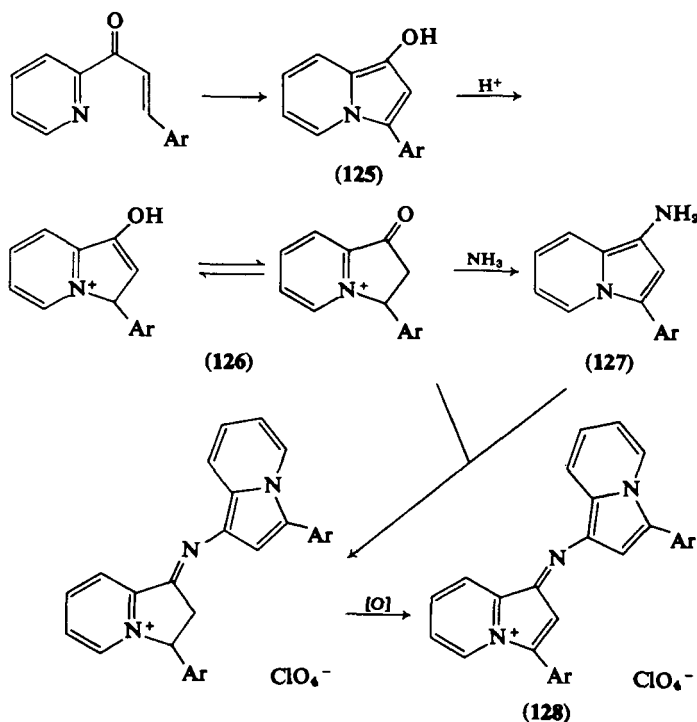


Azacyanine dyes of the form **128** are produced when 2-cinnamoyl pyridine is heated in acetic acid with ammonium acetate and perchlorate¹⁸⁷ (Scheme 16). The initial product is presumed to be a hydroxy-

¹⁸⁶ F. N. Stepanov and L. I. Lukashina, *Zh. Obshch. Khim.* **29**, 2792 (1959) [*CA* **54**, 10993 (1960)].

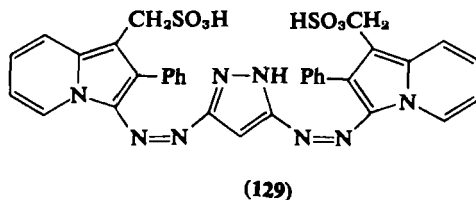
¹⁸⁷ F. Kröck and F. Kröhnke, *Chem. Ber.* **104**, 1645 (1971).

indolizine (125) that tautomerizes under acid conditions,⁷⁹ and some is converted into the amino compound 127. Reaction between 126 and 127 leads to 128.



SCHEME 16

Not surprisingly, azo derivatives of indolizines are readily prepared since the aryl diazonium ion is a good electrophile. Many compounds of this type (e.g., 129¹⁸⁸) have been synthesized,^{183,188,189} some of which are used as dyes.¹⁹⁰

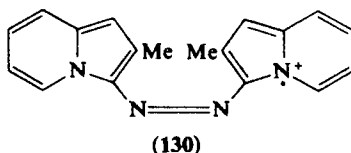


¹⁸⁸ J. Bailey, British Patent 1,156,496 (1969) [CA 71, 92638 (1969)].

¹⁸⁹ L. Pentimalli, *Boll. Sci. Fac. Chim. Ind. Bologna* 23, 15 (1965) [CA 64, 6789 (1966)].

¹⁹⁰ L. Pentimalli, L. Greci, and G. Milani, *Ann. Chim. (Rome)* 63, 95 (1973).

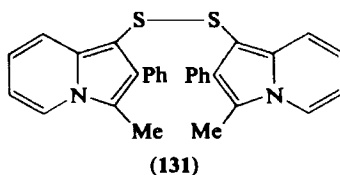
Another method of preparing azobisindolizines is by reaction with tosyl or picryl azide.¹⁹¹⁻¹⁹³ 2-Methylindolizine is converted into the 3,3'-bisazo compound after 2 minutes. The product yields the radical ion **130** (detected by EPR) when treated with 1 mole of silver perchlorate.^{194,195} The redox characteristics of such compounds have been studied by Hünig and co-workers.^{196,197} In view of the instability of aminoindolizines, they have not been used to prepare diazonium salts. 1-Nitrosoindolizines, however, yield diazonium nitrates in good yield when treated with dry nitric oxide.^{182,198} The products are stable both in



solution and the solid state. The low infrared $\text{N}\equiv\text{N}$ stretching frequency at 2140 cm^{-1} has been taken as evidence of extensive delocalization (cf. $\text{PhN}_2^+\text{BF}_4^-$, 2296 cm^{-1}).

6. Sulfide Derivatives

Glover and his associates have synthesized a number of bisheterocyclic compounds linked by a mono- or disulfide bridge.⁹ 2-Phenyl-2-methylindolizine with sulfur monochloride gave, among other compounds, **131** in 46% yield.



¹⁹¹ A. S. Bailey, M. C. Churn, and J. T. Wedgwood, *Tetrahedron Lett.*, 5953 (1968).

¹⁹² A. S. Bailey, B. R. Brown, and M. C. Churn, *J. Chem. Soc. C*, 1590 (1971).

¹⁹³ M. Colonna, L. Greci, and G. Padovano, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis. Rend.* **7**, 84 (1970) [*CA* **75**, 76510 (1971)].

¹⁹⁴ M. Colonna, L. Greci, P. Bruni, and G. Padovano, *Gazz. Chim. Ital.* **101**, 396 (1971).

¹⁹⁵ M. Colonna, L. Greci, and P. Bruni, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis. Rend.* **8**, 112 (1970-1971) [*CA* **80**, 107666 (1974)].

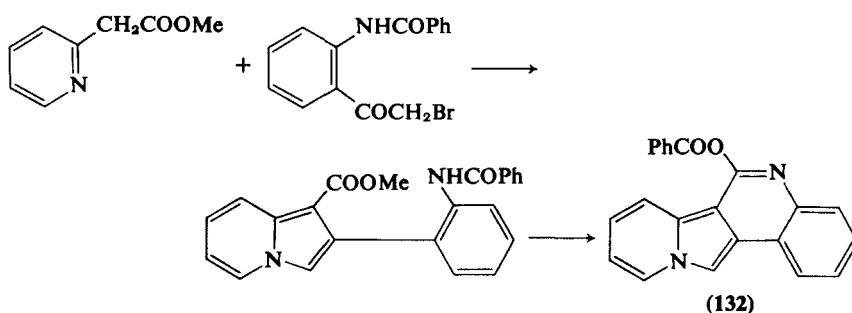
¹⁹⁶ S. Hünig, G. Kiesslich, F. Linhart, and H. Schlaf, *Ann.* **752**, 182 (1971).

¹⁹⁷ S. Hünig, G. Kiesslich, F. Linhart, and H. Schlaf, *Ann.* **752**, 196 (1971).

¹⁹⁸ J. M. Tedder and K. H. Todd, *J. Chem. Soc., Chem. Commun.*, 424 (1967).

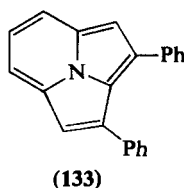
B. CYCLIZATIONS

This section is concerned with reactions that result in the fusion of one or more additional rings to the indolizine system. Of course, an indolizine synthesis can be designed in which the functional groups are oriented for cyclization. An example is the formation of the indolizino-[1,2-*c*]quinoline **132** (Scheme 17).¹⁹⁹



SCHEME 17

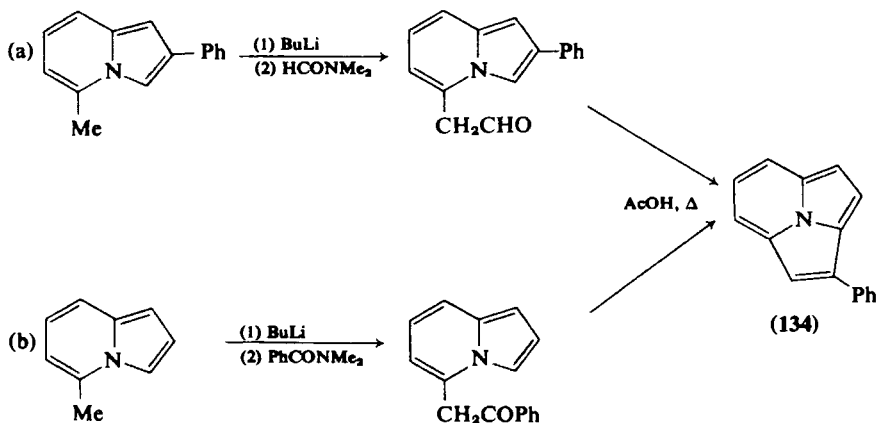
Cyclazines are an interesting class of compounds that can be synthesized by intramolecular cyclization to the 3-position of the indolizine ring.²⁰⁰ The reactivity of the methyl group in 5-methylindolizine is similar to that in 2-picoline, and this provides the means of preparing cycl[3,2,2]azines. Thus, the reaction of 5-methyl-2-phenylindolizine with butyl lithium followed by *N,N*-dimethylbenzamide yielded the 5-(phenacyl) derivative, which could be ring-closed to **133** by heating



with acetic acid. The formation of a cyclazine **134** was demonstrated unambiguously by routes (a) and (b) given in Scheme 18.

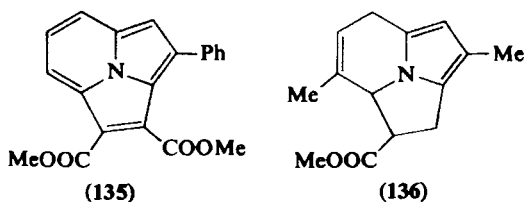
¹⁹⁹ G. Niederdellman and F. Kröhnke, *Ann.* **688**, 196 (1965).

²⁰⁰ R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *J. Am. Chem. Soc.* **81**, 1459 (1959).



SCHEME 18

Cycl[3,2,2]azines are also obtained from cycloaddition of indolizines with DMAD.^{60,201} This is illustrated by the reaction of 2-phenylindolizine with DMAD which gives **135**. Hydrolysis with methanolic potassium hydroxide gives the corresponding acid, which can be decarboxylated using copper chromite.



Substituted indolizines have been shown to undergo cycloadditions with suitably substituted alkenes to give pyrroloindolizines.²⁰² Thus, 2,6-dimethylindolizine with methyl acrylate gives **136**. The reactions presumably involve [8 + 2] cycloadditions, with subsequent 1,5-proton shifts.

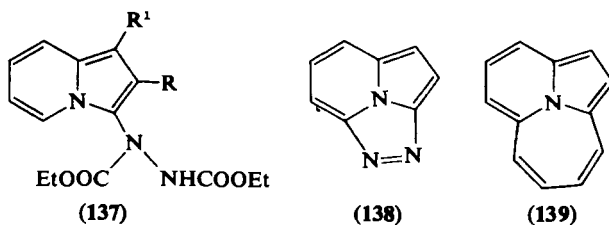
The reaction of ethyl azodicarboxylate with indolizines has been reported to give substituted products such as **137** in high yield.²⁰³ This type of reaction has also been reviewed.²⁰⁴

²⁰¹ A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.* **24**, 582 (1959).

²⁰² S. Ikeda, S. Kajigasshi, and S. Kanamasa, *Chem. Lett.*, 367 (1976) [*CA* **85**, 21048 (1976)].

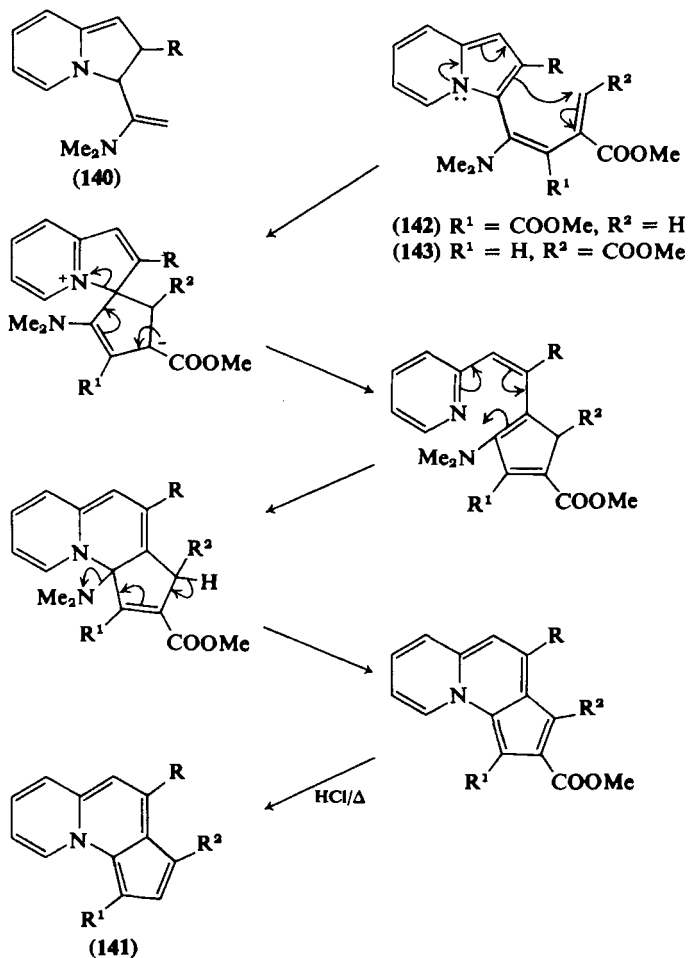
²⁰³ M. Colonna, P. Bruni, and A. Monti, *Gazz. Chim. Ital.* **94**, 509 (1964).

²⁰⁴ M. Colonna and A. Monti, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis. Rend.* **251**, 13 (1962-1963) [*CA* **62**, 16177 (1965)].



No formation of the diazacycl[3,2,2]azine system (138) was reported.

During attempts to prepare the cycl[4,3,2]azine system (139) by reaction of the enamine (140) with DMAD, the cyclopenta[*c*]quinolizine (141) was formed.¹⁶⁵ Two intermediates of suggested structures 142

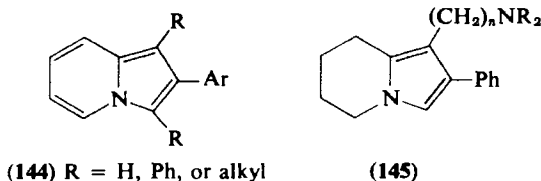


SCHEME 19

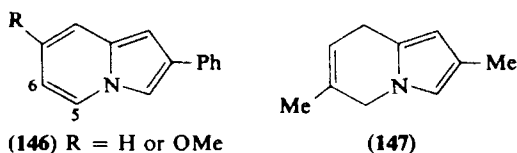
and **143** were isolated, which led the authors to propose the mechanism shown in Scheme 19 for the unusual indolizine \rightarrow quinolizine rearrangement.

C. REDUCTION

Substituted indolizines such as **144** may be hydrogenated to their 5,6,7,8-tetrahydro derivatives using Raney nickel or occasionally platinum catalysts at ambient temperature and pressure.^{151,152,205} A series of derivatives of the type **145** were found to have various kinds of CNS activity.²⁰⁵



Workers at Keele University have investigated the reduction of indolizines by dissolving metals.²⁰⁶ Indolizine itself gave mixtures of 5,6-dihydro and 5,6,7,8-tetrahydro derivatives with sodium in ethanol or liquid ammonia, but with **146** the 5,6-dihydro product was obtained in good yield. Reduction of 2-methylindolizine with sodium in ethanol gave a mixture of products, whereas 2,6-dimethylindolizine gave a single product that was assigned structure **147** on the basis of its NMR spectrum.



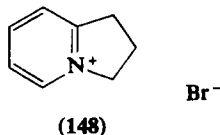
Both the fully unsaturated and the hydrogenated alkyl indolizines were rather unstable in air. Attempted carbene additions to the relatively stable 2-phenyldihydro compounds proved unsuccessful.

The pyrrole ring of indolizine can be selectively reduced to **148** by catalytic hydrogenation using palladium/charcoal in aqueous hydrogen bromide.²⁰⁷

²⁰⁵ L. A. Walter and P. Margolis, *J. Med. Chem.* **10**, 498 (1967).

²⁰⁶ G. R. Cliff, G. Jones, and J. Stanyer, *J. Chem. Soc. C*, 3426 (1971).

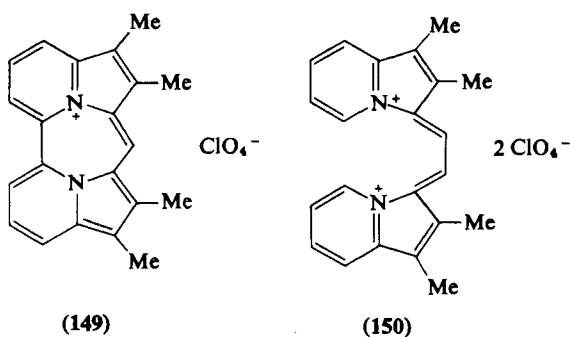
²⁰⁷ O. G. Lowe and L. C. King, *J. Org. Chem.* **24**, 1200 (1959).



It is almost certain that the *1H*- or *3H*-indolizinium cation is formed initially.

D. OXIDATION

Although the indolizine nucleus is readily oxidized, no *N*-oxides have been isolated.²⁰⁸ Ring fission often occurs, and the reaction has been used in the past for structure elucidation.⁴ Consequently, oxidation reactions have only generated interest where the ring remains intact. One such oxidation that has been investigated in detail is that of 3,3'-methylene diindolizines (prepared from the reaction of indolizines with formaldehyde) by chloranil.²⁰⁹ The principal products appear to be 5,5'-bridged compounds such as **149**. The same research group has also studied the condensation of glyoxal with 1,2-dimethylindolizine which gives **150**.²¹⁰



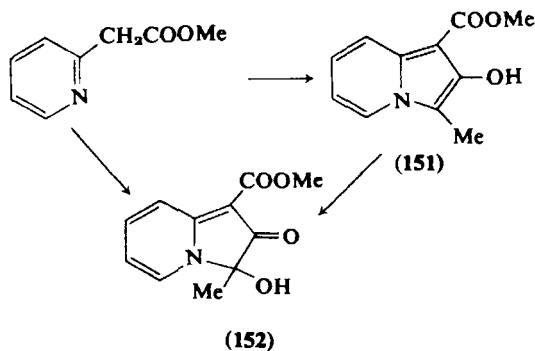
In another example of oxidation without ring fission, the major product obtained from the reaction between methyl 2-pyridylacetate and ethyl- α -bromopropionate was not the expected indolizine **151**, but a compound whose chemical and physical properties suggested the structure **152** (Scheme 20). When the reaction was repeated under

²⁰⁸ H. V. Euler, H. Hasselquist, and O. Heidenberger, *Ark. Kemi* **14**, 419 (1959) [*CA* **54**, 12156 (1960)].

²⁰⁹ M. Fraser, A. Malera, and D. H. Reid, *J. Chem. Soc. B*, 483 (1966).

²¹⁰ M. Fraser and D. H. Reid, *J. Chem. Soc.*, 1421 (1963).

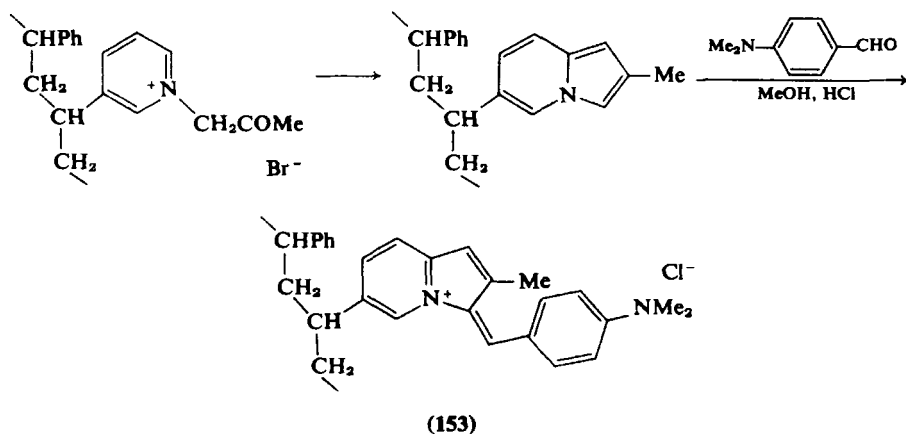
nitrogen, **151** was the product. Treatment of **151** with aqueous potassium ferricyanide at room temperature readily gave **152**.²¹¹



SCHEME 20

E. POLYMERIZATION

Various indolizines containing vinyl groups in the pyridine ring have been synthesized by standard procedures, e.g., Ref. 212. Turchinovich and co-workers found that whereas 2-methyl-6-vinyl- and 1,2-dimethyl-6-vinylindolizine would not polymerize, even in the presence of an initiator, 3-acetyl-1,2-dimethyl-6-vinylindolizine polymerized spon-

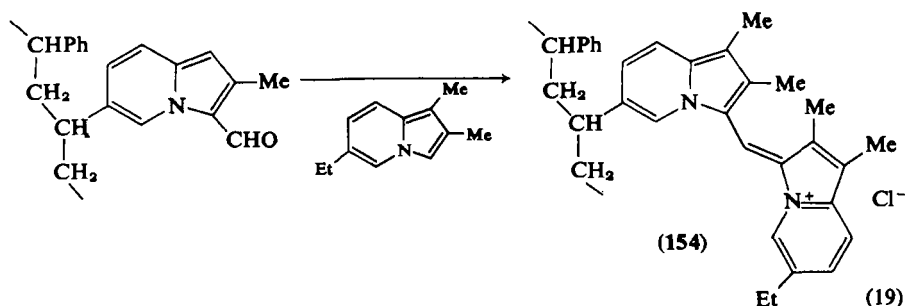


SCHEME 21

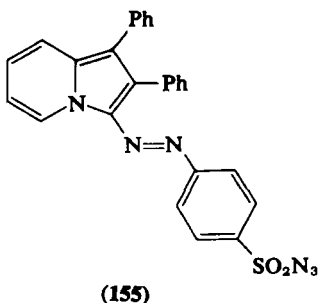
²¹¹ R. J. Bowers and A. G. Brown, *J. Chem. Soc. C*, 1434 (1970).

²¹² F. N. Stepanov and G. Yu. Turchinovich, *Zh. Obshch. Khim.* **32**, 2659 (1962) [*CA* **59**, 7904 (1963)].

taneously and also copolymerized with styrene.^{213,214} For the latter type of polymer, the indolizine ring may be generated *in situ* [see Scheme 21 and Eq. (19)]. Polyindolizine dyes, such as **153** and **154** may be subsequently prepared, and in such reactions all the indolizine nuclei in the polymer undergo condensation.



Indolizine dyes such as **155** have been bound to an ethyl acrylate-acrylic acid copolymer by heating in tetrahydrofuran to give dyes that do not migrate in photographic color film emulsions.²¹⁵



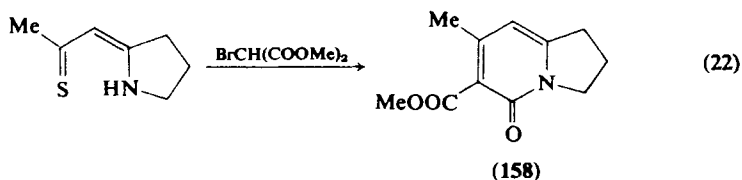
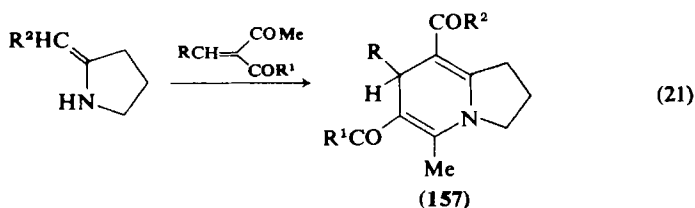
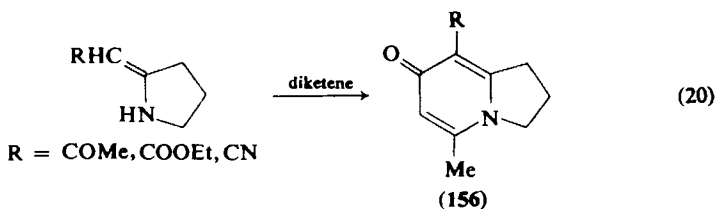
V. Partially Reduced Indolizines

The compounds dealt with in this section are those for which a synthesis leads to a partially reduced system as the major product. Some of these systems appear elsewhere in this review, e.g., Sections II,C and IV,C.

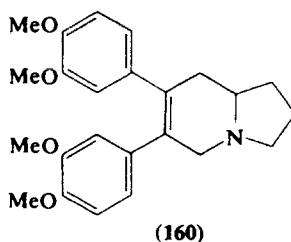
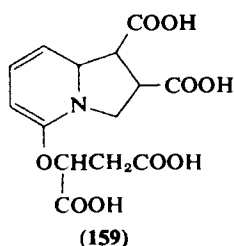
²¹³ F. N. Stepanov and G. Yu. Turchinovich, *Ukr. Khim. Zh.* **30**, 738 (1964) [CA **61**, 13480 (1964)].

²¹⁴ G. Yu. Turchinovich, *Tr. Kiev. Politekhn. Inst.* **43**, 91 (1963) [CA **62**, 10558 (1965)].

²¹⁵ C. Holstead, *Ger. Offen.* **2,122,025** (1971) [CA **76**, 40242 (1972)].



1,2,3,7-Tetrahydro derivatives, such as compounds **156–158**, some possessing biological activity, have been prepared by the routes shown in Eqs. (20)–(22).^{216–219} Another compound with a reduced pyrrole ring is the product obtained from the reaction of *N*-methyl-2-pyridone with maleic anhydride, formulated as the (unlikely) structure **159**. It is very labile, dissociating to *N*-methyl-2-pyridone and maleic acid in polar solvents.²²⁰



²¹⁶ T. Kato and T. Hozumi, *Yakugaku Zasshi* **93**, 1084 (1973) [*CA* **79**, 105033 (1973)].

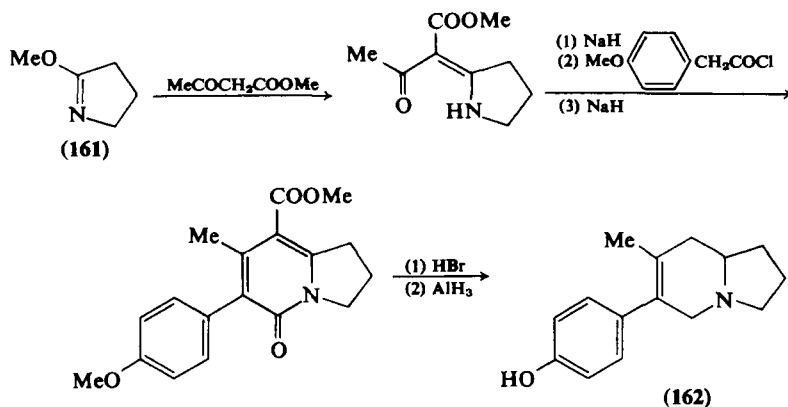
²¹⁷ H. Meyer, F. Bossert, W. Vater, and K. Stöpel, Ger. Offen. 2,210,633 (1973) [*CA* **79**, 146519 (1973)].

²¹⁸ S. Danishefsky and S. J. Etheredge, *J. Org. Chem.* **39**, 3430 (1974).

²¹⁹ W. Fuhrer, R. Hobi, A. Pfaltz, and P. Schneider, *Helv. Chim. Acta* **57**, 1498 (1974).

²²⁰ B. S. Thyagarajan and K. Rajagopalan, *Tetrahedron* **19**, 1483 (1963).

The structure of septicine (**160**)²²¹ one of the relatively few naturally occurring compounds in which the indolizine ring system is not part of a larger fused-ring system, was recently confirmed by synthesis.^{222,223} The *Ipomoea* group of alkaloids also possess a partially hydrogenated indolizine ring. Two of these are ipalbine and its aglycone, ipalbidine (**162**), which has been synthesized from the pyrroline **161** as shown in Scheme 22.²²⁴ Numerous other syntheses of indolizine alkaloids are reviewed regularly in Ref. 1.



SCHEME 22

Indolizines with a saturated six-membered ring may be obtained from pyrrole or furan derivatives.^{225,226} The reaction of 3,4-dimethylpyrrolmagnesium bromide with γ -chlorobutyronitrile followed by dilute acid gave 5,6,7,8-tetrahydro-1,2-dimethyl-5-oxoindolizine. 5,6,7,8-Tetrahydroindolizine can be obtained by the cyclodehydration of 3-(2-furyl)propylamine over alumina at 400°C. The same product is obtained by the treatment of 3-(2-pyrrolyl)propyl cyanide with hydrogen chloride in the presence of boron trifluoride etherate catalyst, followed by Wolff-Kishner reduction of the intermediate ketone.

²²¹ J. H. Russel, *Naturwissenschaften* **50**, 443 (1963).

²²² T. R. Govindachari and N. Viswanathan, *Tetrahedron* **26**, 715 (1970).

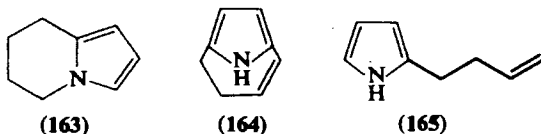
²²³ R. B. Herbert, F. B. Jackson, and I. T. Nicholson, *J. Chem. Soc., Chem. Commun.*, 450 (1976).

²²⁴ A. E. Wick, P. A. Bartlett, and D. Dolphin, *Helv. Chim. Acta* **54**, 513 (1971).

²²⁵ H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.*, 98 (1962).

²²⁶ J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.* **27**, 1652 (1962).

The pyrolysis of a number of cycloalkano[*a*]pyrroles including **163** has been investigated.²²⁶ The major products from the latter were suggested to be **164** and **165**.



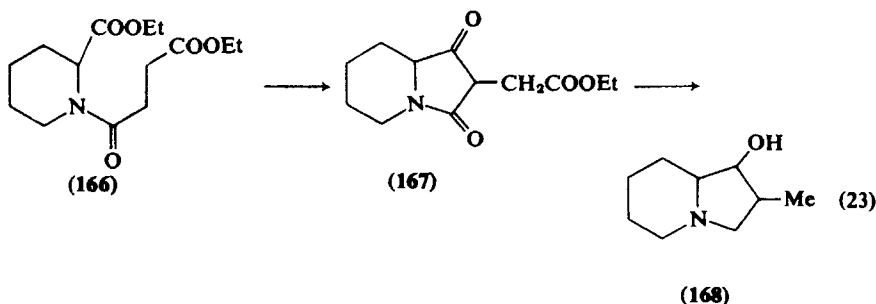
VI. Indolizidines

A. SYNTHETIC METHODS

Methods of obtaining the fully reduced system have, as might be expected, changed less over the past 18 years than those for the aromatic nucleus. Only new methods or modifications of existing ones will be covered here.

1. Variations on Existing Routes

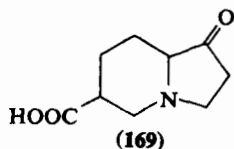
Most of the possible oxoindolizidines have been prepared by the application of the Dieckmann reaction to various piperidyl and pyrrolidinyl diesters. Winterfeldt and Hoffstadt used it to convert **166** into **167** in good yield.²²⁷ Alkaline hydrolysis followed by lithium aluminum hydride reduction gave the alcohol **168** [Eq. (23)].



A recently reported total synthesis of *dl*-camptothecin was based on 1-oxooctahydroindolizine-6-carboxylic acid (**169**).²²⁸ To accomplish the

²²⁷ K. Winterfeldt and W. Hoffstadt, *Arch. Pharm. (Weinheim)* **303**, 812 (1970).

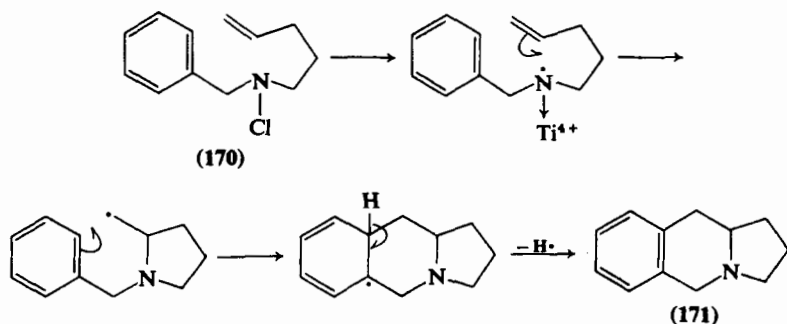
²²⁸ C. S. F. Tang, C. J. Morrow, and H. Rapoport, *J. Am. Chem. Soc.* **97**, 159 (1975).



synthesis of the above intermediate, isocinchomeronic acid (pyridine-2,5-dicarboxylic acid) was hydrogenated in the presence of 5% rhodium on alumina. The piperidine analog was then converted into the diethyl ester, which with ethyl 3-bromopropionate in the presence of sodium acetate gave ethyl 3-(2,5-diethoxycarbonylpiperidino)-propionate. The required acid was then obtained by Dieckmann cyclization of the triester, followed by hydrolysis and decarboxylation.

Indolizidine itself can be obtained by the action of *N*-chlorosuccinimide on 2-propylpiperidine, followed by sulfuric acid in the presence of ultraviolet light.⁴ Grundon and Reynolds suggested that this reaction gave a poor yield because the mechanism involved abstraction of a hydrogen atom from a terminal methyl group and that, if this group were substituted, better yields would result. They demonstrated this by converting *N*-chloro-2-butylpiperidine into 3-methylindolizidine in 64% yield. Moreover, the reaction was stereospecific, giving almost entirely one diastereoisomer.²²⁹

Surzur and Stella, in a paper mainly concerned with the free radical cyclization of pyrrolizidines, reported the formation of the benzindolizidine **171** from *N*-benzyl-*N*-chloropentenylamine (**170**) when treated with titanium(III) chloride in aqueous acetic acid (Scheme 23).²³⁰



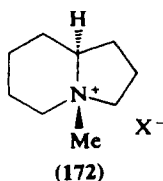
SCHEME 23

²²⁹ M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 3898 (1963).

²³⁰ J.-M. Surzur and L. Stella, *Tetrahedron Lett.*, 2191 (1974).

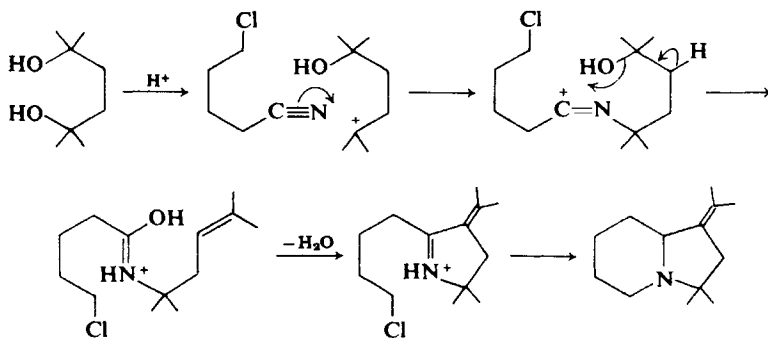
2. Transannular Reactions

Indolizidine has been made in 68% yield by the action of silver ions on *N*-chloroazacyclononane in dioxane.²³¹ Pyrrolizidine and quinolizidine have been prepared similarly but in much poorer yields. Also, 1-methyl-5-hydroxyazacyclononane gave a *trans*-fused quaternary salt (172) when heated with either perchloric, hydriodic, or picric acid in ethanol.²³² However, it is more usual to apply this reaction in the reverse direction for synthesis of medium ring compounds.



3. Miscellaneous Methods

An important new route to indolizidine starts from 2-(3-hydroxypropyl)tetrahydrofuran, which is converted via the chloro and cyano compounds into the amine. This is then cyclized to indolizidine in good yield with an alumina/zirconium dioxide catalyst. The 6-methyl derivative has also been prepared as a mixture of isomers from 2-(3-hydroxybutyl)-tetrahydrofuran.²³³



SCHEME 24

²³¹ O. E. Edwards, D. Vocelle, J. ApSimon, and F. Haque, *J. Am. Chem. Soc.* **87**, 678 (1965).

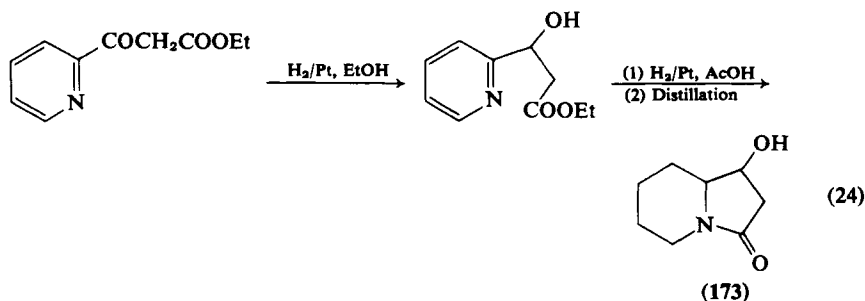
²³² A. J. Sisti and D. L. Sohner, *J. Org. Chem.* **32**, 2026 (1967).

²³³ I. M. Skvortsov, E. A. Zadumina, and A. A. Ponomarev, *Khim. Geterotsikl. Soedin.*, 864 (1965) [*CA* **64**, 12643 (1966)].

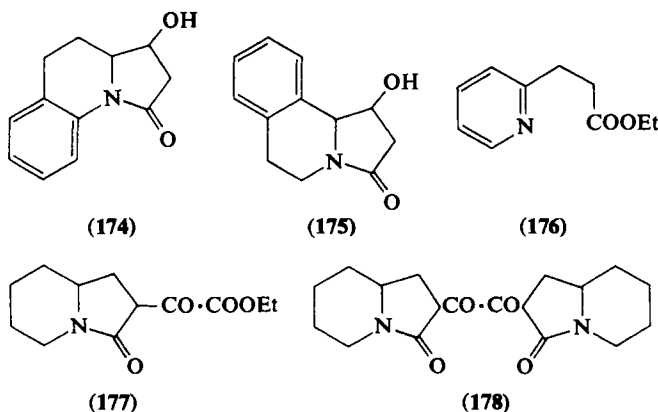
An entirely different synthesis, due to Meyers and Libano, involves the acid-catalyzed condensation of a ditertiary glycol with an ω -chloronitrile. The resulting ω -chloroalkylpyrroline is reduced with aqueous sodium borohydride and cyclized by steam distillation under basic conditions.²³⁴ An example of this route is given in Scheme 24.

Several reductive cyclizations have been used to obtain the indolizidine system⁴ of which the route shown in Eq. (24), used by Carelli and his associates, is an example.²³⁵

Both geometrical isomers of **173** were isolated. Similar reactions in the quinoline and isoquinoline series gave **174** and **175**, respectively. Some of these products exhibited hypnotic and sedative activity.



Winterfeldt and Erning achieved the one-step conversion of **176** into the indolizidine **177** by a dissolving-metal reduction in the presence of diethyl oxalate.²³⁶ Treatment of the piperidine analog with sodium ethoxide and diethyl oxalate gave 10% of the dimer **178**.

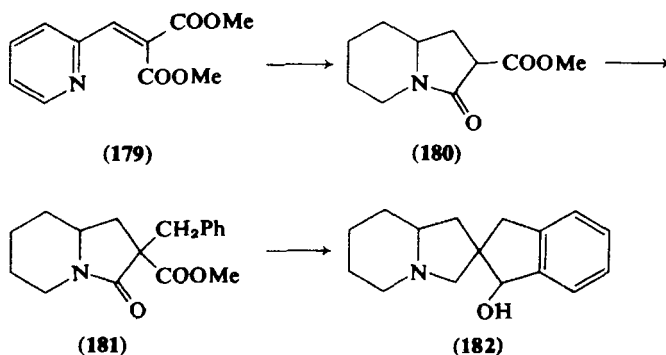


²³⁴ A. Meyers and W. Y. Libano, *J. Org. Chem.* **26**, 4399 (1961).

²³⁵ V. Carelli, F. Liberatore, and F. Morlacchi, *Ann. Chim. (Rome)* **51**, 467 (1961).

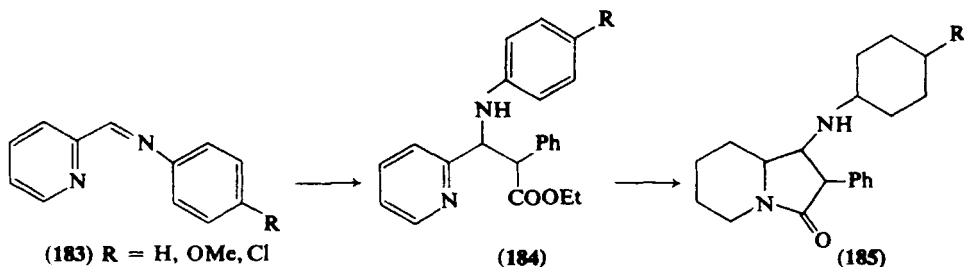
²³⁶ K. Winterfeldt and W. Erning, *Arch. Pharm. (Weinheim)* **298**, 220 (1965).

A third example of a reductive cyclization method is illustrated by the preparation of the indolizidine **180** (Scheme 25), which is among a large number of 3-oxindolizidines described in a series of pharmaceutical patents by Mohrbacher.²³⁷⁻²⁴² The condensation of pyridine-2-carboxaldehyde with dimethyl malonate gave **179**. This was converted into **180** by reduction using a platinum catalyst in ethanolic acetic acid. Reaction of **180** with sodium hydride followed by benzyl chloride gave **181**. Ring closure with polyphosphoric acid followed by reduction with lithium aluminum hydride gave the spiro derivative **182**, which is claimed to have anti-inflammatory properties.



SCHEME 25

The pyridine derivatives (**183**) underwent addition reactions with ethyl phenylacetate to give adducts **184**, which could be reductively cyclized in the presence of a platinum catalyst, to give the indolizidines **185**.²⁴³



²³⁷ R. Mohrbacher, U.S. Patent 3,189,611 (1965) [CA 63, 11514 (1965)].

²³⁸ R. Mohrbacher, U.S. Patent 3,245,991 (1966) [CA 64, 17558 (1966)].

²³⁹ R. Mohrbacher, U.S. Patent 3,245,990 (1966) [CA 64, 19563 (1966)].

²⁴⁰ R. Mohrbacher, U.S. Patent 3,268,540 (1966) [CA 65, 15352 (1966)].

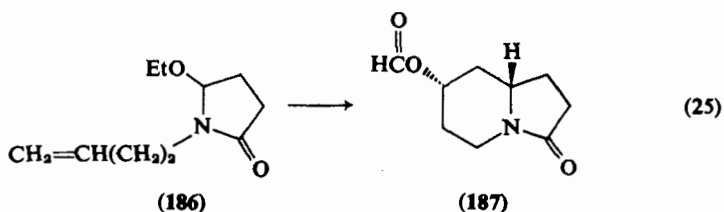
²⁴¹ R. Mohrbacher, U.S. Patent 3,274,202 (1966) [CA 66, 2475 (1967)].

²⁴² R. Mohrbacher, U.S. Patent 3,297,704 (1967) [CA 67, 100020 (1967)].

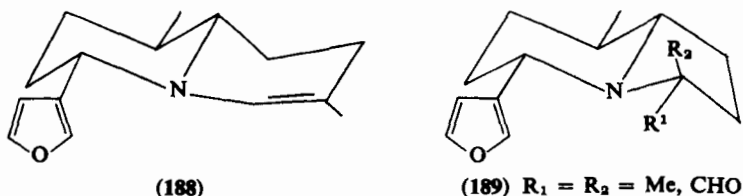
²⁴³ J. M. Sprake and K. D. Watson, *J. Chem. Soc., Perkin Trans. 1*, 5 (1976).

Another means of ring closure is cyclodehydration, and among other reagents, *N,N*-dimethylphosphodichloridate has been used. 3-(2-Piperidyl)propanol and 3-(2-piperidyl)pentanol were smoothly converted into indolizidine and 1-ethylindolizidine, respectively, using this reagent.²⁴⁴

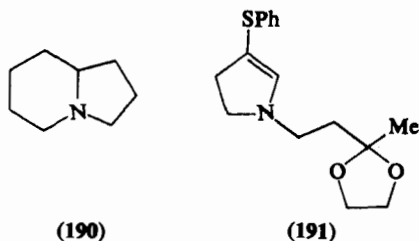
Formic acid has been used to cyclize ethoxylactams to indolizidines.^{245,246} Thus, **186** was converted stereospecifically into **187** [Eq. (25)].²⁴⁵



The reaction of a quinolizidine enamine, 6-dehydrodeoxynupharidine (**188**) with *p*-toluenesulfonyl chloride in benzene gave two epimeric indolizidine carboxaldehydes (**189**).²⁴⁷



The recent synthesis of (\pm) δ -coniceine (**190**) involved a pyrroline derivative (**191**) as a key intermediate as it was relatively stable. It was cyclized with methanolic hydrogen chloride, desulfurized with Raney



²⁴⁴ K. Winterfeldt and W. Muller, *Arch. Pharm. (Weinheim)* **297**, 740 (1964).

²⁴⁵ J. Dijkink and W. N. Speckamp, *Tetrahedron Lett.*, 4047 (1975).

²⁴⁶ J. Dijkink, H. E. Schoemaker, and W. N. Speckamp, *Tetrahedron Lett.*, 4043 (1975).

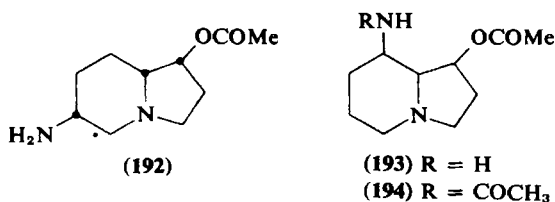
²⁴⁷ R. T. LaLonde, A. I. M. Tsai, and C. Wong, *J. Org. Chem.* **41**, 2514 (1976).

nickel, and finally converted into **190** by acid hydrolysis and Wolff-Kishner reduction.²⁴⁸

Intramolecular cyclization of activated aminoalkyl cyclopropanes to corresponding oxindolizidines has been achieved.²⁴⁹

4. Stereoselective Syntheses

Much of the work on naturally occurring indolizidines falls into the above class, because the compounds are normally single stereoisomers. Such a compound is the alkaloid, slaframine (**192**) present in the fungus *Rhizoctonia leguminicola*, and believed to be a salivation factor in cattle. Rinehart and co-workers successfully synthesized 6-acetamido-1-acetoxyindolizidine as a mixture of diastereoisomers, all four of which were isolated by chromatography, and one shown to be identical to *N*-acetylslaframine.²⁵⁰ Structure **193** had previously been assigned to slaframine.²⁵¹ To resolve this situation, Rinehart synthesized **194** and demonstrated that, whereas the product was spectroscopically very similar to *N*-acetylslaframine, it was clearly different in its chromatographic behavior. More recently, a stereoselective synthesis of slaframine has been achieved by Gensler and Hu.²⁵²



During attempts to synthesize a series of optically active, bicyclic α -aminoketones (**195–198**), Kuneida and co-workers found that racemization invariably took place during the saponification and decarboxylation of the β -ketoester intermediates, prepared via Dieckmann reactions [Eqs. (26) and (27)].²⁵³

²⁴⁸ R. V. Stevens, Y. Luh, and J.-T. Sheu, *Tetrahedron Lett.*, 3799 (1976).

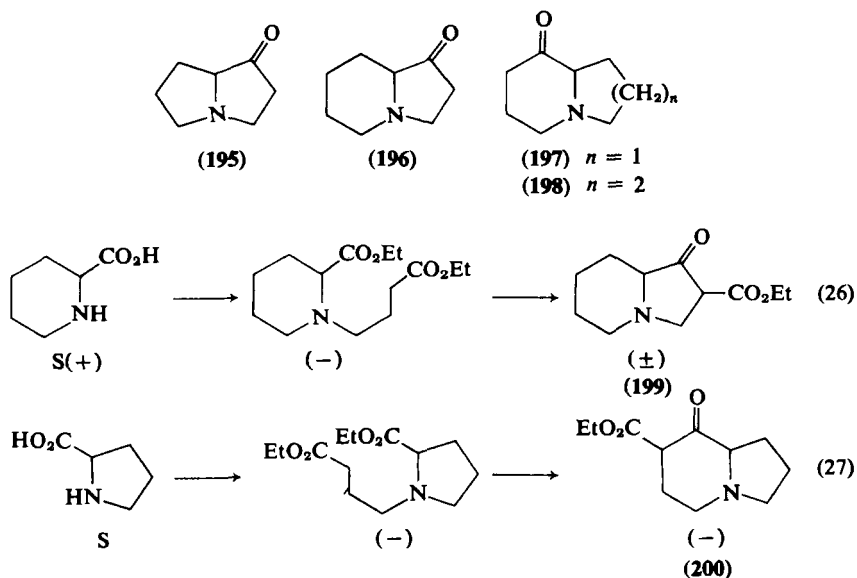
²⁴⁹ S. Danishefsky and J. Dynak, *J. Org. Chem.* **39**, 1979 (1974).

²⁵⁰ K. K. Rinehart, D. Cartwright, and R. A. Gardiner, *J. Am. Chem. Soc.* **92**, 7615 (1970).

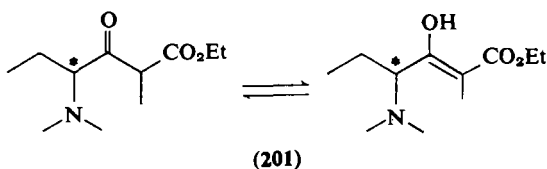
²⁵¹ B. J. Whitlock, D. P. Rainey, N. V. Riggs, and F. M. Strong, *Tetrahedron Lett.*, 3819 (1966).

²⁵² W. J. Gensler and M. W. Hu, *J. Org. Chem.* **38**, 3848 (1973).

²⁵³ T. Kuneida, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* **15**, 337 (1967).

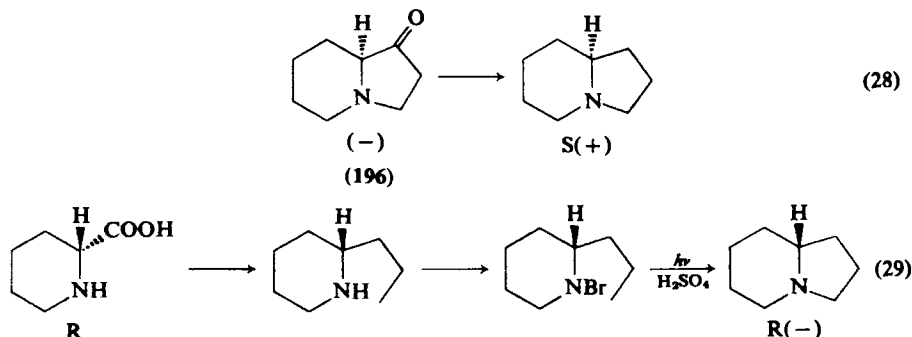


Of compounds **199** and **200**, only **200** could be obtained in its optically active form, but on treatment with hydrochloric acid even this was racemized. It was suggested that the β -ketoesters retained their optical activity because of the preferential enolization (**201**).



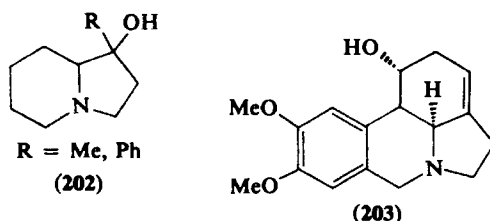
After decarboxylation, enolization in the alternative mode would cause racemization. However, this reasoning does not explain why **199** was racemized. The racemic α -aminoketones were eventually resolved via their bromocamphorsulfonates. Optically pure $(-)$ -indolizidin-1-one (**196**) was reduced with lithium aluminum hydride to the alcohol, tosylated, and again reduced to $(+)$ -indolizidine [Eq. (28)]. Since indolizidine obtained from *R*-pipecolic acid [Eq. (29)] was levorotatory, it followed that the absolute configuration of the original ketone was *S*.²⁵⁴ The optical rotatory dispersion (ORD) curve of the *S*($-$)-ketone showed a strong negative Cotton effect as predicted by the octant rule.

²⁵⁴ S. Yamada and T. Kuneida, *Chem. Pharm. Bull.* **15**, 490 (1967).



In an investigation of the effect of structure on biological activity, Hibbett and Sam separated the epimeric alcohols **202** obtained by Grignard reactions on the ketone.²⁵⁵ The structural assignments were made on the basis of physical constants, infrared and NMR data, and pK_a values.

In the course of attempts to synthesize the nonaromatic moieties of alkaloids such as pluviine (**203**), Wenkert and collaborators have developed the route to indolizidines shown in Scheme 26.²⁵⁶ Quaterni-



zation of methyl nicotinate with the bromoketal **204** gave a salt that was reduced to the piperidine, then cyclized with ethereal hydrogen chloride to **205**. A Dieckmann reaction on the indolizidine gave the β -diketone **206**, which with methanolic sulfuric acid gave a single enol ether (**207**).

Recently, a glandular secretion of the Pharaoh ant has been isolated and identified as 3-butyl-5-methylindolizidine.²⁵⁷ Oliver and Sonnet have successfully synthesized its four stereoisomers.^{258,259} Routes are shown in Scheme 27.²⁵⁸

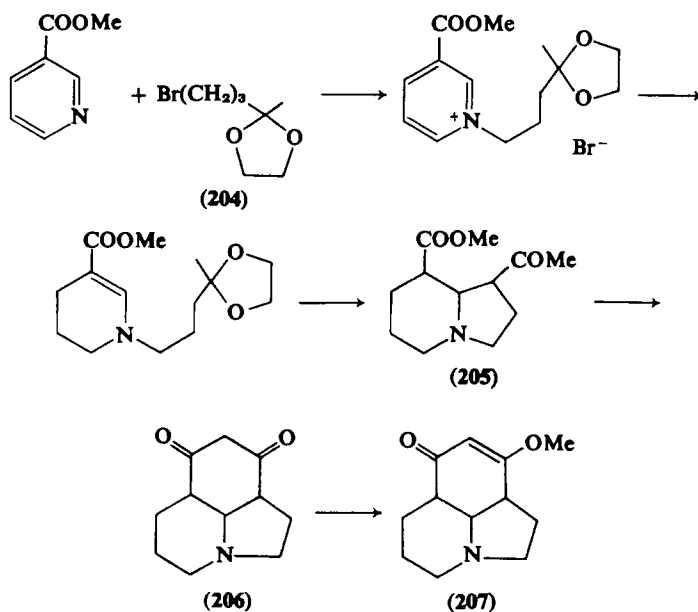
²⁵⁵ E. P. Hibbett and J. Sam, *J. Heterocycl. Chem.* **7**, 857 (1970).

²⁵⁶ E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Am. Chem. Soc.* **90**, 6177 (1968).

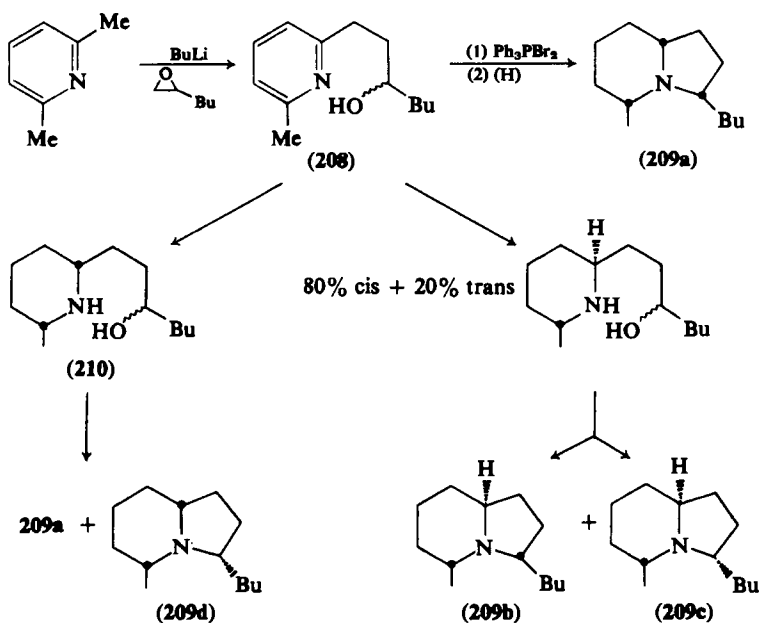
²⁵⁷ F. J. Ritter, I. Rotgans, E. Talman, P. Verwiël, and F. Stein, *Experientia* **29**, 530 (1973).

²⁵⁸ J. E. Oliver and P. E. Sonnet, *J. Org. Chem.* **39**, 2662 (1974).

²⁵⁹ P. E. Sonnet and J. E. Oliver, *J. Heterocycl. Chem.* **12**, 289 (1975).



SCHEME 26



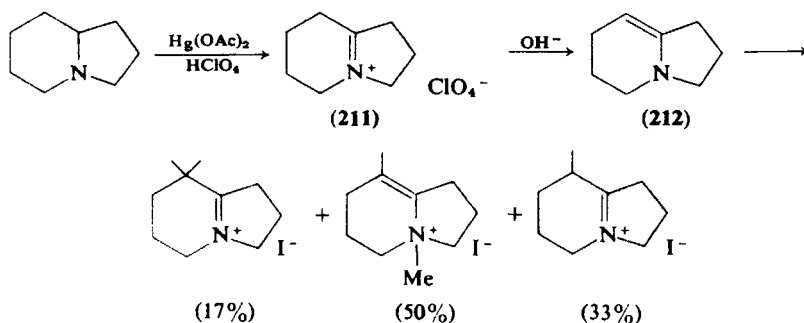
SCHEME 27

Triphenylphosphine dibromide cyclization of **208** followed by catalytic hydrogenation of the pyridinium salt gave the all-*cis* isomer **209a**, whereas sodium-in-ethanol reduction gave a mixture of isomers from which the *trans* isomer was isolated and cyclized to give **209b** and **209c**. The remaining isomer **209d** was separated by spinning-band distillation from a mixture with **209a** obtained from the cyclization of **210**. Additional work has been published.^{260,261}

B. REACTIONS

Apart from the normal reactions of tertiary aliphatic amines, indolizidines undergo reactions at the carbon atoms adjacent to the nitrogen, and particularly at the bridgehead carbon.

Reinecke and Kray have done much work on the reactions of indolizidine enamines, obtained as shown in Scheme 28.²⁶²⁻²⁶⁶ In an investigation of the methylation of **212** with methyl iodide, they found that C-methylation took place first in preference to N-methylation, in contrast to the corresponding quinolizidine enamine, presumably because of the greater steric strain of a tetrahedral nitrogen atom in a five-membered ring.²⁶²



SCHEME 28

²⁶⁰ E. Talman, F. J. Ritter, and P. E. J. Verwiel, *Mass Spectrom. Biochem. Med. Symp.*, 197 (1973).

²⁶¹ F. J. Ritter, Ger. Offen. 2,418,595 (1974) [*CA* **82**, 72779 (1975)].

²⁶² M. Reinecke and L. R. Kray, *J. Org. Chem.* **30**, 3671 (1965).

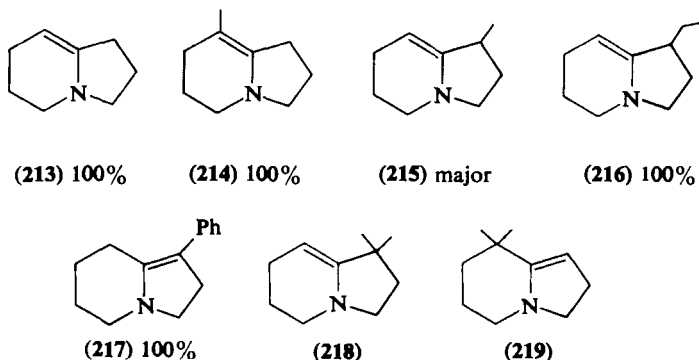
²⁶³ M. Reinecke and L. R. Kray, *J. Org. Chem.* **31**, 4215 (1966).

²⁶⁴ M. Reinecke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965).

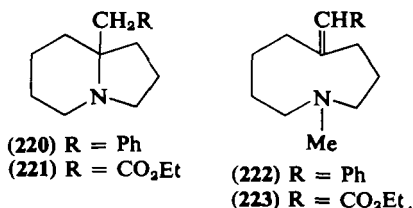
²⁶⁵ M. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.* **37**, 3489 (1972).

²⁶⁶ M. Reinecke and R. F. Francis, *J. Org. Chem.* **37**, 3494 (1972).

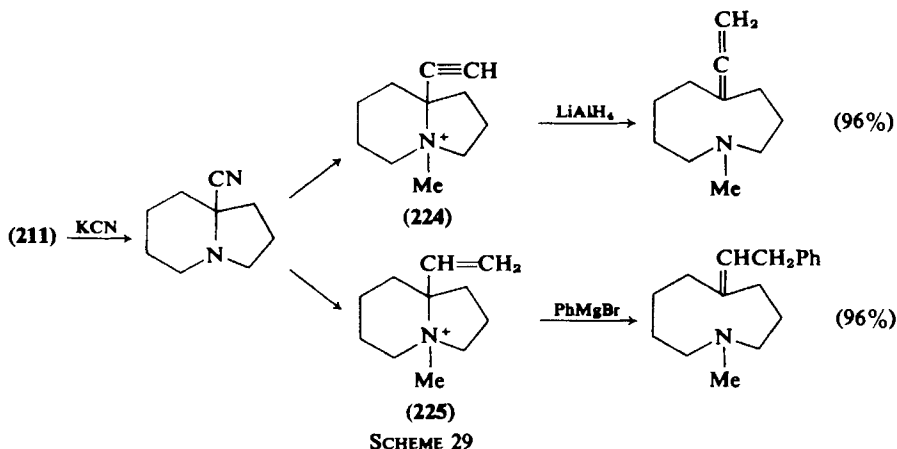
The positions of the double bonds in such enamines appear to be controlled by the same factors that affect the stability of simple olefins and not by those which affect the enamines from many cyclic ketones.²⁶³ The products of mercuric acetate oxidation of some indolizidines, with yields, are shown in structures **213–217**. The double bond positions were ascertained by comparing the IR and NMR spectra with **218** and **219**.



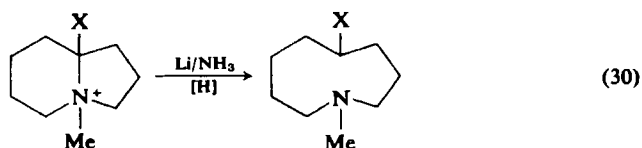
Treatment of the iminium salt **211** with a nucleophile led to indolizidines substituted at C-9.²⁶⁴ Thus, reaction with benzylmagnesium chloride and with ethyl bromoacetate and zinc gave **220** and **221**, respectively. Treatment of **220** and **221** with methyl iodide yielded the corresponding methiodide salts. Reaction with base resulted in β -elimination and ring opening with the formation of **222** and **223**. This is a most important reaction of indolizidines since it provides a good route to medium-ring heterocyclic compounds. It was found that sodamide as the base gave only products with exocyclic double bonds, whereas sodium ethoxide gave in addition some endocyclic double bond products.²⁶⁵



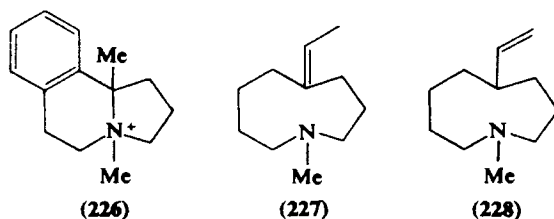
Ring opening was also achieved by substitution at the bridgehead with a vinyl or acetylene group (using $\text{CH}_2=\text{CHMgCl}$ or $\text{CH}\equiv\text{CMgBr}$) followed by reaction with a Grignard reagent or lithium aluminum hydride (Scheme 29).²⁶⁶



A third method of ring opening investigated by Reinecke and his associates was Emde cleavage,²⁶⁶ which may be generally represented as in Eq. (30), where X is a group that can stabilize the intermediate carbanion, e.g., Ph or COMe. In these cases, there was no evidence for peripheral C-N fission as has been found in **226**.

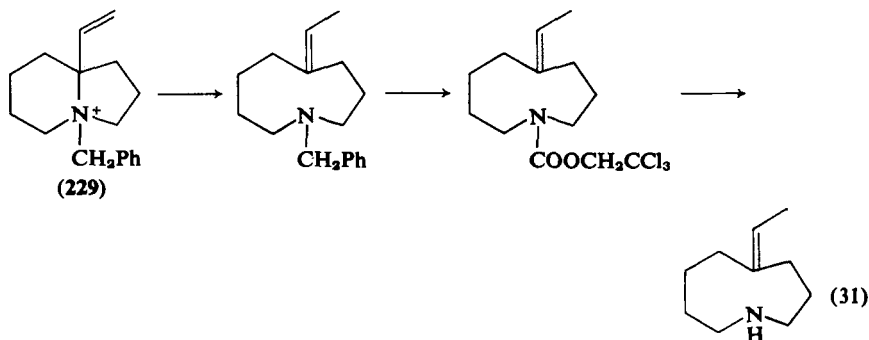


The lithium aluminum hydride reduction of **225** afforded two products, namely **227** and **228**. Emde reduction, however, gave only **227**. By contrast, lithium aluminum hydride gave a single product from **224**, but lithium in liquid ammonia produced multiple products. Thus either method may be selective, depending on the nature of X. The Emde method has also been applied to 9-cyanoindolizidines with the formation of medium-ring amides.²⁶⁷

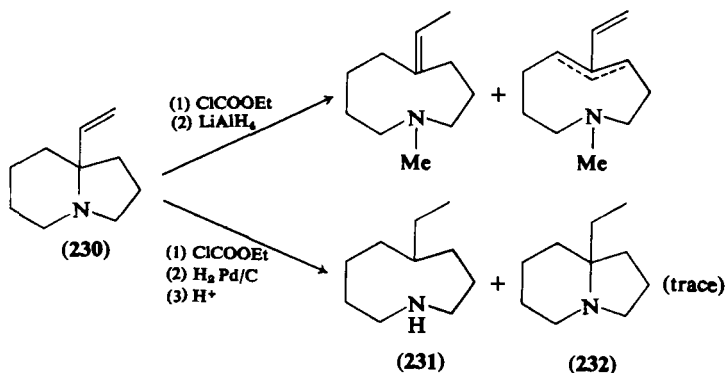


²⁶⁷ Y. Arata, T. Kobayashi, M. Nakamura, and T. Yasuda, *Yakugaku Zasshi* **90**, 1424 (1970) [CA **74**, 76306 (1971)].

The reactions described so far all yield medium-ring tertiary amines. Reinecke's group have recently extended their methods to synthesize the more useful secondary amines.²⁶⁸ Three syntheses were developed. The first [Eq. (31)] involves reductive cleavage of the benzyl indolizidinium salt **229** with lithium aluminum hydride, followed by replacement of the benzyl group with the labile trichloroethoxycarbonyl group. The latter may be removed under mild conditions with zinc-methanol, which does not cause migration of the double bond.



Reaction of **230** with ethyl chloroformate gave a mixture of ring-opened compounds that could be reduced with lithium aluminum hydride or catalytically (Scheme 30); the latter method provides a secondary amine (**231**) as the major product.



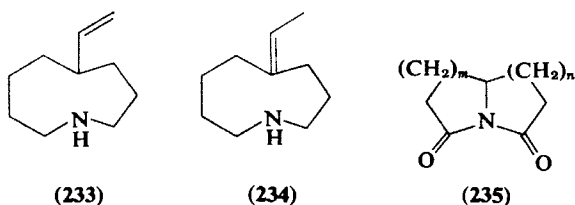
SCHEME 30

²⁶⁸ M. Reinecke and R. G. Daubert, *J. Org. Chem.* **38**, 3281 (1973).

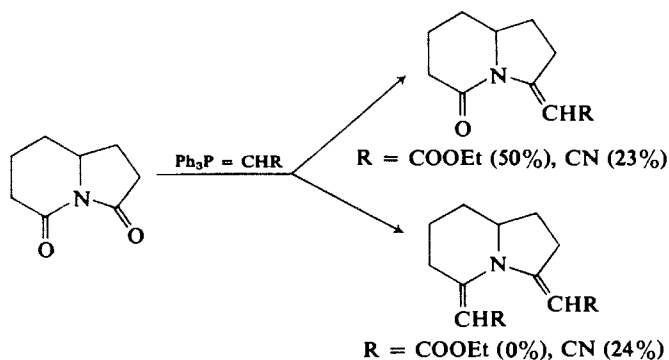
The third method was based on the reductive cleavage of allyl groups from *N*-allyl-*N*-alkylanilines, employing lithium aluminum hydride and nickel chloride.²⁶⁹ Treatment of **230** with these reagents gave a mixture of products, identified as **231**–**234**.

With a large excess of lithium aluminum hydride, the major product was **231**, but the unsaturated ring-opened compounds could not be obtained in a pure state. Thus the trichloroethylcarbamate method would appear to be the one of choice.

Flitsch and co-workers have studied cyclic imides of general formula **235** including indolizidine-3,5-dione.^{270–272} The effect of ring size on the



UV spectra²⁷⁰ and on the mode of ring cleavage by base²⁷¹ was investigated. In the case of indolizidine dione, the six-membered ring opens to give a γ -lactam. The Wittig reaction was also examined and some selectivity could be obtained, depending on the phosphorane used (Scheme 31).²⁷²



SCHEME 31

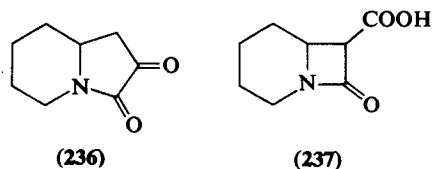
²⁶⁹ V. L. Tweedie and J. C. Allabashi, *J. Org. Chem.* **26**, 3676 (1961).

²⁷⁰ W. Flitsch, *Chem. Ber.* **97**, 1548 (1964).

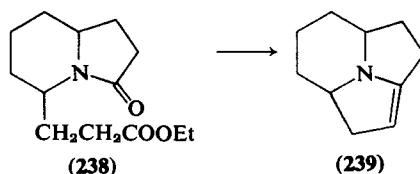
²⁷¹ W. Flitsch, *Chem. Ber.* **97**, 1542 (1964).

²⁷² W. Flitsch and B. Mürer, *Chem. Ber.* **104**, 2852 (1971).

Another indolizidinedione, the 2,3-isomer **236**, synthesized by a standard Dieckmann procedure, was converted by periodate into the β -lactam **237**, which has been patented as an intermediate in penicillin or cephalosporin syntheses.^{273,274}



The formation of cycl[3,2,2]azines from indolizines has its parallel in the saturated system with a reaction reported by Japanese workers.²⁷⁵ The indolizidinone ester **238** gives the tricyclic compound **239** on distillation with soda lime. This reaction is of potential importance in view of the number of alkaloids containing fused systems similar to **239**.



C. STEREOCHEMISTRY OF INDOLIZIDINES

Because of the possibility of nitrogen inversion, *cis*- and *trans*-fused indolizidine have no separate chemical identity. However, conformational analysis of the indolizidine and quinolizidine systems suggests that the *trans* is significantly more stable than the *cis* conformation. A value for the energy difference of 2.4 kcal mole⁻¹ has been obtained, compared with ca. 0.3 kcal mole⁻¹ for hydrindane.^{276,277}

The presence of Bohlmann bands in the infrared 2700 cm⁻¹ region has been used as evidence of a *trans*-fused conformation in quinolizidines.²⁷⁸ These bands appear to be present when two or more C-H

²⁷³ H. Rapoport, Ger. Offen. 2,130,730 (1971) [CA 76, 99688 (1972)].

²⁷⁴ D. R. Bender, R. F. Bjeldanes, D. R. Knap, and H. Rapoport, *J. Org. Chem.* **40**, 1264 (1975).

²⁷⁵ I. Murakoshi, K. Takada, and J. Haginawa, *Yakugaku Zasshi* **89**, 1661 (1969) [CA 72, 55217 (1970)].

²⁷⁶ H. S. Aaron, *Chem. Ind. (London)* **30**, 1338 (1965).

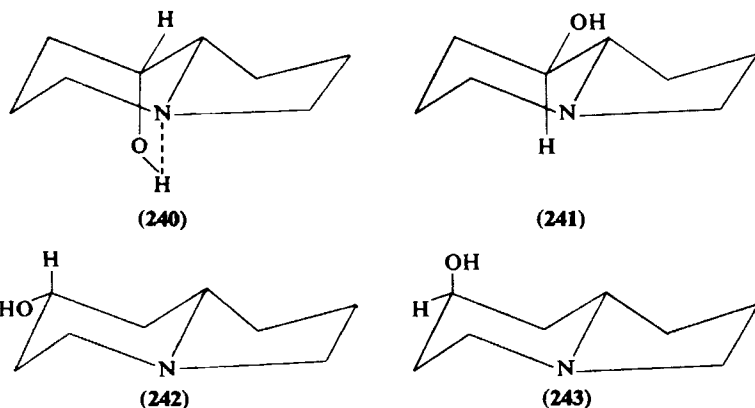
²⁷⁷ H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968).

²⁷⁸ F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).

bonds bear a *trans*-diaxial relationship to the N lone pair.²⁷⁹ Theobald and Lingard examined the infrared spectra of 3,3'-dideuterio and 9-deuterioindolizidine and found a decrease in intensity of the Bohlmann bands of 33 and 28%, respectively.²⁸⁰ They concluded that the presence of such bands is a good indication of a *trans* conformation for indolizidines.

A calculation of the heat and free energy of the conformational isomerization of indolizidine has also been made by Russian workers.²⁸¹

Aaron's group has studied various hydroxy derivatives of both indolizidines and pyrrolizidines and assigned conformations, mainly on the basis of infrared data. The isomers of 8- (**240**, **241**) and 7-hydroxy-indolizidine (**242**, **243**) were separated as racemates after chemical or catalytic reduction of the ketones.²⁸²



In the spectra of dilute solutions, only **240** shows intramolecular hydrogen bonding, and all four isomers show strong Bohlmann bands. Hence all were assigned *trans*-ring conformations. These conformations were further supported by (i) NMR data—primarily the chemical shift and bandwidth of the carbinol proton; (ii) pK_a values—**240** was found to be considerably more basic than **241**, whereas there was less difference between the 7-hydroxy compounds; (iii) chemical data—the product isomer ratios obtained when the conditions for the reduction of the ketones were altered were in accordance with the above assignments. The

²⁷⁹ F. Bohlmann, D. Schumann, and M. Schulz, *Tetrahedron Lett.*, 173 (1965).

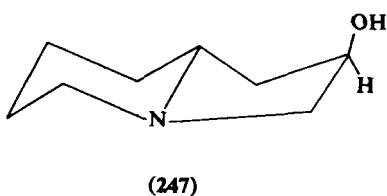
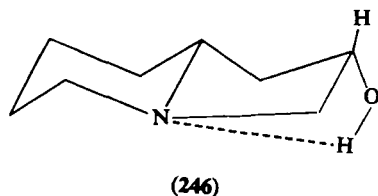
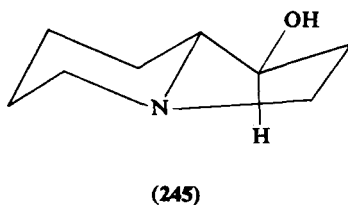
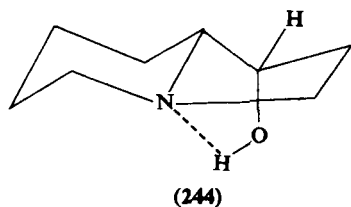
²⁸⁰ A. E. Theobald and R. G. Lingard, *Spectrochim. Acta, Part A* **24**, 1245 (1968).

²⁸¹ I. M. Skvortsov, V. V. Tarasov, I. V. Antipova, V. M. Levin, S. A. Kolesnikov, and I. Evtushenko, *Mater. Vses. Konf. Din. Stereokhim. Konformatsionnomu. Anal.*, 1st., 94 (1970, published 1971) [*CA* **80**, 107865 (1974)].

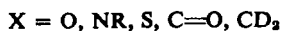
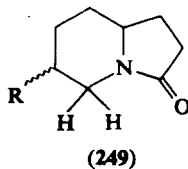
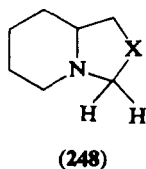
²⁸² C. P. Rader, R. L. Young, and H. S. Aaron, *J. Org. Chem.* **30**, 1536 (1965).

greater stability of the *trans*-ring fusion is demonstrated particularly by **241** where one might expect the *cis* conformer to be stabilized by intramolecular bonding. In a long path-length cell, 3% of the *cis* form was detected.²⁷⁷

Parallel results were obtained for the 1- and 2-hydroxy compounds for which the dominant conformations appear to be **244–247**.²⁸³



The configurations and conformations of the four epimers of 5,7-dimethylindolizidine have also been assigned.²⁸⁴ Workers at Portsmouth Polytechnic have investigated the conformational equilibria of a large number of bridgehead nitrogen systems including indolizidines, and their work, together with that of others in the field, has been reviewed.²⁸⁵ They have obtained conformational information by deducing the orientation of adjacent heteroatom lone pairs from geminal coupling constants in systems of the type **248** and **249**.^{286–288} There is evidence that the 6-membered ring of **249** ($R = \text{Me}$) exists in a deformed chair conformation.²⁸⁷



²⁸³ H. S. Aaron, C. P. Rader, and G. E. Wicks, *J. Org. Chem.* **31**, 3502 (1966).

²⁸⁴ B. Luning and C. Lundin, *Acta Chem. Scand.* **21**, 2136 (1967).

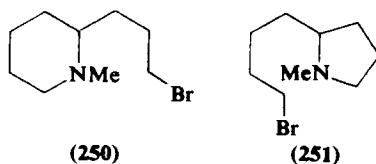
²⁸⁵ T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.* **71**, 109 (1971).

²⁸⁶ R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magn. Reson.* **3**, 263 (1971).

²⁸⁷ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **5**, 295 (1973).

²⁸⁸ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **4**, 259 (1972).

The stereochemistry of indolizidine and pyrrolizidine metho salts was studied by Meyer and Sapianchiay.²⁸⁹ They found that methylation of indolizidine gave a 50:50 mixture of isomers from which only the *cis*-metho salt could be obtained pure. Cyclization of either **250** or **251** gave only the *cis* isomer, which can be accounted for on the basis of less



steric strain during ring closure, particularly for **250**. The assignments were based on the chemical shifts of the methyl groups ($6.88 \tau = \textit{cis}$ and $7.18 \tau = \textit{trans}$) by comparison with compounds whose stereochemistry was known unequivocally.

²⁸⁹ W. L. Meyer and N. Sapianchiay, *J. Am. Chem. Soc.* **86**, 3343 (1964).

Olefin Synthesis with Anils

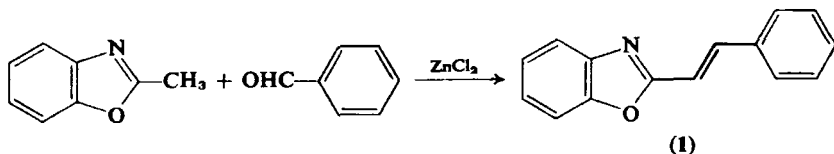
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*Research and Development Department, Dyestuffs and Chemicals Division,
Ciba-Geigy Ltd., Basle, Switzerland*

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I. Introduction

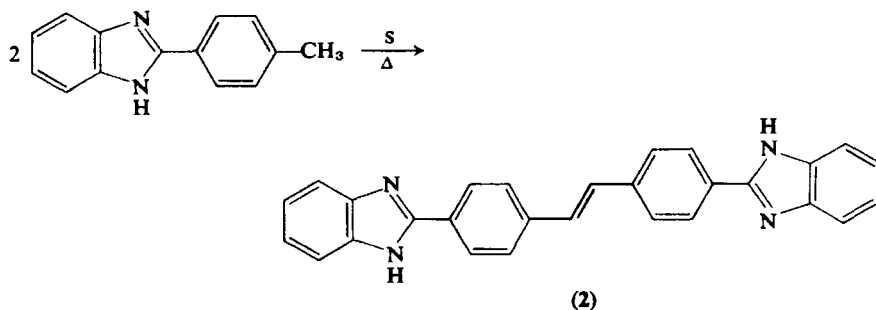
The preparation of heterocyclic-substituted ethylene derivatives by direct condensation of aldehydes with activated methyl groups, as, for example, in the formation of 2-styrylbenzoxazole (1) has long been known.¹ However, the analogous reaction of aldehydes with those



heterocycles in which the heterocyclic ring is separated from the methyl group by a 1,4-phenylene bridge has not been reported.

In recent years, the technical importance of stilbenyl heterocycles has rapidly increased as a result of the application of products particularly such as fluorescent whitening agents.^{2,3}

The previously available methods for the preparation of such compounds were somewhat limited in their application. First, the oxidative coupling of 2 molecules of a heterocyclic-substituted toluene derivative in the presence of sulfur results in the formation of symmetrical stilbenes,^{4,5} as shown by the synthesis of 4,4'-bis(benzimidazol-2-yl)stilbene (2). The disadvantages of this method are the high reaction temperatures necessary and the difficulties often involved in product workup.



¹ D. M. Brown and G. A. R. Kon, *J. Chem. Soc.*, 2147 (1948).

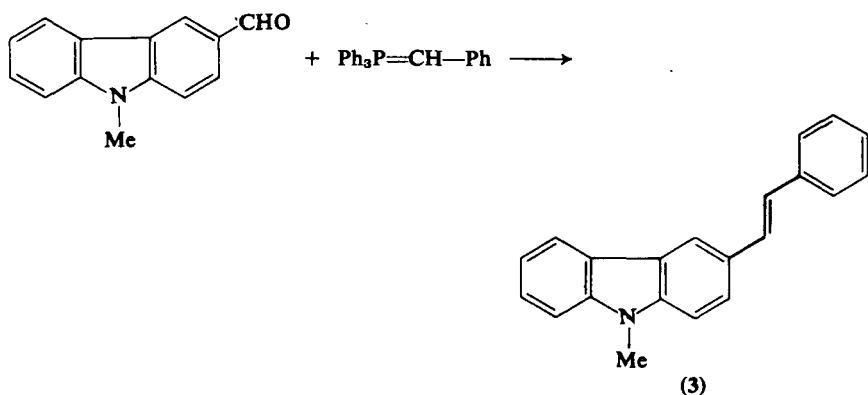
² H. Gold, "The Chemistry of Synthetic Dyes" (K. Venkataraman, ed.), Vol. 5, pp. 535-679. Academic Press, New York, 1971.

³ R. Anliker and G. Müller, in "Environmental Quality and Safety" (F. Coulston and F. Korte, eds.), Suppl. Vol. IV. Thieme, Stuttgart, 1975.

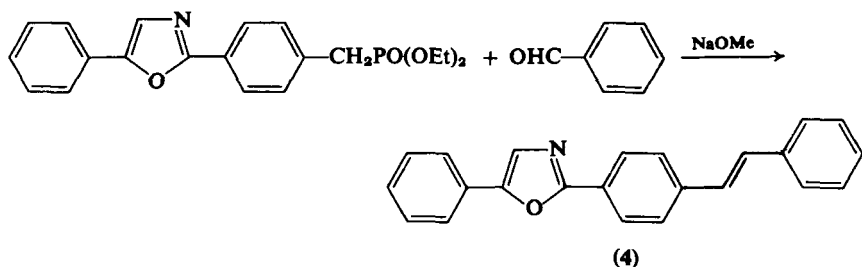
⁴ N. N. Crouse (Sterling Drug Inc.), British Patent 861,240 (U.S. Appl. 1958).

⁵ A. E. Siegrist, E. Maeder, L. Guglielmetti, and P. Liechti (Ciba-Geigy AG), U.S. Patent 3,413,233 (Swiss Appl. 1964).

A second method involves the well-known Wittig reaction, one example of which is the preparation⁶ of *N*-methyl-3-styrylcarbazole (3) from the corresponding 3-formyl-*N*-methylcarbazole.



Finally, the Horner reaction has also been applied to the preparation of heterocyclic stilbenes, as illustrated by the formation of the 2-(stilben-4-yl)oxazole (4).⁷



The chief disadvantage of the last two methods is that starting materials containing relatively reactive functional groups are required, which are often difficult to obtain.

The reaction sequence described herein enables the preparation of heteroaromatic stilbenes by direct condensation of methyl or methylene groups with anils derived from aromatic aldehydes, in the presence of strong base, and in certain dipolar aprotic solvents.

In this chapter the development, the possible mechanism, and the conditions for the reaction, are briefly discussed, followed by a survey

⁶ G. Drefahl, G. Ploetner, and A. Ziegler, *Chem. Ber.* **95**, 2775 (1962).

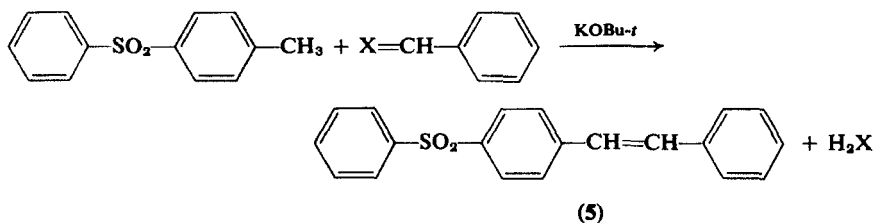
⁷ V. I. Grigoreva and B. M. Krasovickii, *Khim. Geterotsikl. Soedin.*, 761 (1967) [*CA* **68**, 78179 (1968)].

of the various heterocyclic systems to which reactions of this type have been applied.

II. Condensation of Anils with Methyl Groups

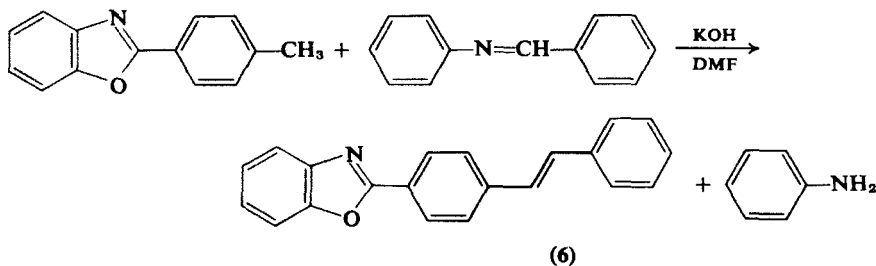
A. PREVIOUS WORK AND DEVELOPMENT

In 1964 it was shown by Becker⁸ that the condensation of phenyl *p*-tolyl sulfone to *p*-phenylsulfonyl stilbene (5) proceeded more readily and in improved yield when the reaction was carried out using benzal-aniline rather than benzaldehyde.⁹ This original observation was



X = O, 40% yield in dimethyl sulfoxide (DMSO)
 = N-Ph, 84% yield in dimethylformamide (DMF)

followed¹⁰ in 1965 by the application of benzalaniline in DMF to the preparation of 2-(stilben-4-yl)benzoxazole (6) from 2-(*p*-tolyl)benzoxazole. It was further recognized that this reaction was not restricted solely to the benzoxazole series. A number of other nitrogen-containing heteroaromatic systems carrying methyl groups, either in the form of *p*-tolyl substituents, or, in the case of condensed heterocycles, bonded



⁸ H.-D. Becker, *J. Org. Chem.* **29**, 2891 (1964).

⁹ G. A. Russell and H.-D. Becker, *J. Am. Chem. Soc.* **85**, 3406 (1963).

¹⁰ A. E. Siegrist, P. Liechti, E. Maeder, L. Guglielmetti, H. R. Meyer, and K. Weber (Ciba-Geigy AG), U.S. Patents 3,725,395 and 3,732,221 (Swiss Appl. 1965 and 1966).

directly to the benzo ring, have also been observed to undergo reaction.^{10,11}

The wide applicability that this reaction has since found has led to the process becoming known as the "Anil Synthesis," an expression that will be used in the following text as a general description.

B. THE EFFECT OF BASE

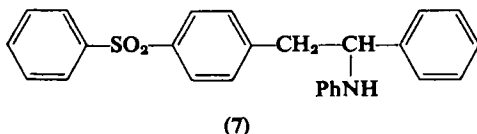
The base that has commonly been used in such reactions is potassium *t*-butoxide. However, it is also interesting, particularly from a technical point of view, to note that finely powdered potassium hydroxide, which always contains 10–15% water, is successful in most cases, although, to obtain good yields, 4–8 equivalents of potassium hydroxide per reacting methyl group are required.

That reaction occurs with potassium hydroxide is surprising, as it was previously suggested by Becker⁸ that the success of the synthesis with anils as opposed to the use of the corresponding aldehydes was due to the anhydrous conditions resulting from formation of aniline instead of water during the reaction.

A further explanation may lie in the superior properties of anilines as leaving groups when compared with water. This idea has, however, been disputed^{11,12} and a complex reaction involving all four components of the system suggested.

It has been reported¹¹ that the alkali metal cation plays an important role. Thus, potassium as well as rubidium and cesium salts appears to be superior to those of sodium and lithium.

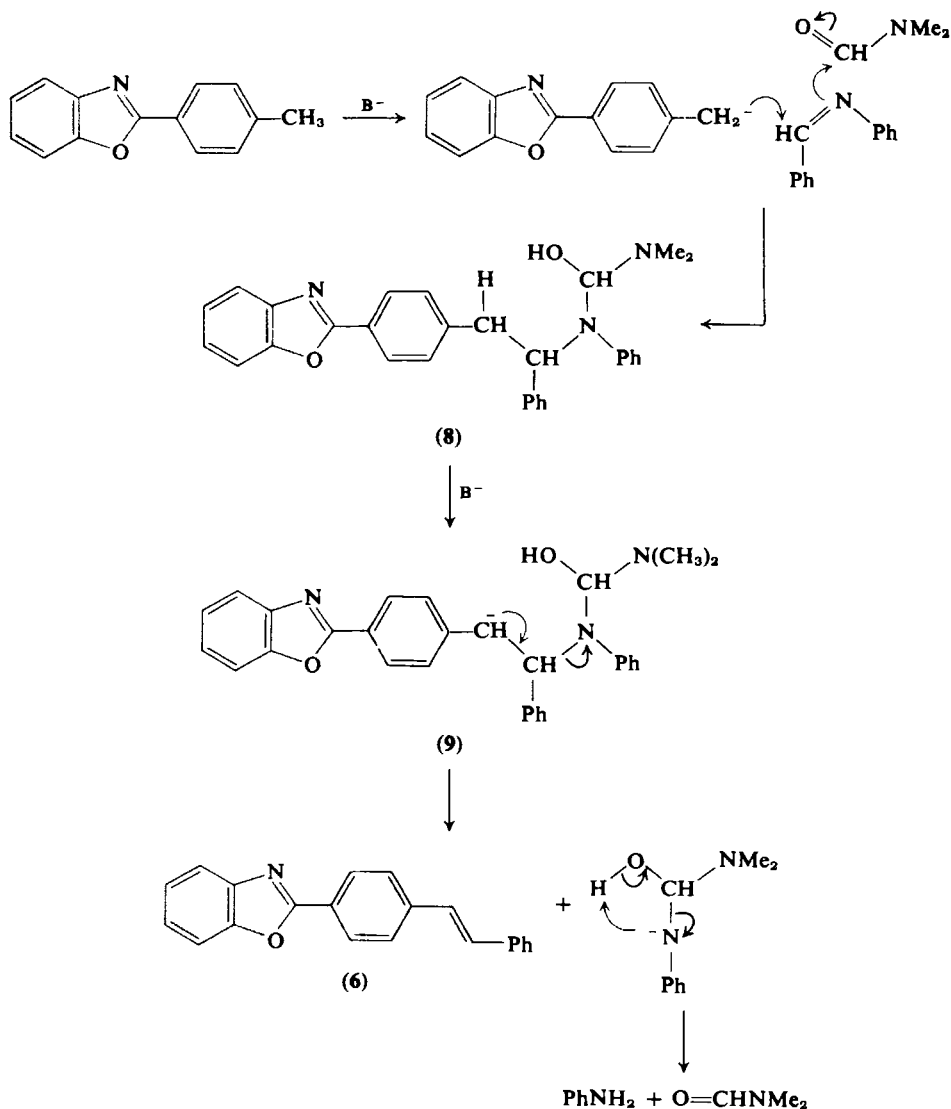
That the base strength is decisive has also been shown by Becker.⁸ The replacement of potassium *t*-butoxide in the reaction of phenyl *p*-tolyl sulfone with benzalaniline by sodium methoxide resulted in the isolation of the addition product 7. This reaction is possible because the



base is sufficiently strong to generate the primary carbanion leading to the addition product (cf. compound 8 in Scheme 1), but not to generate the secondary carbanion required for the elimination (e.g., 9 in Scheme 1).

¹¹ A. E. Siegrist, *Helv. Chim. Acta* **50**, 906 (1967).

¹² W. Sahm, E. Schinzel, and P. Juerges, *Justus Liebigs Ann. Chem.*, 523 (1974).



SCHEME 1

C. THE EFFECT OF SOLVENT

Despite the fact that reaction has been found¹¹ to take place in a number of dipolar aprotic solvents, it would appear that the use of DMF is of prime importance. Thus, in other amides of similar dielectric

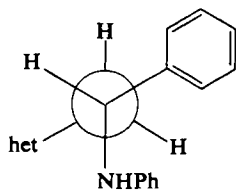
constant, such as dimethylacetamide, hexamethyl phosphoric triamide and even diethylformamide, longer reaction times and higher temperatures were necessary, which led to a reduction in yield. In formamide, methylformamide, and tetramethylurea, no reaction occurred. Becker⁸ has shown that dimethylsulfoxide is unsuitable, since, in the presence of strong base, it undergoes reaction with benzaldehyde anils.

D. MECHANISM AND STEREOCHEMISTRY

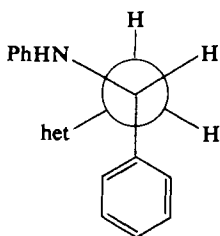
The previously mentioned specific effect of DMF as solvent suggests that it may play an integral role in the reaction, and a possible mechanism for the catalytic action of DMF is shown in Scheme 1.

Furthermore, potassium hydroxide, which is virtually insoluble in DMF, acts as a far superior base than does sodium methoxide, being almost as effective as potassium *t*-butoxide. Hence, it has been suggested^{11,12} that the effective base is a complex derived from DMF and Schiff's base with potassium hydroxide, which then is soluble.

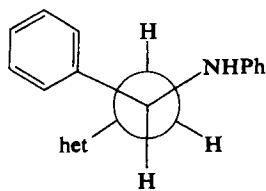
The stereochemical course of the Anil Synthesis is such that exclusive formation of *trans* products has been observed.¹¹ This can be explained by consideration of the conformations of the intermediate addition product. The Newman projections (10a-c) represent the three possible extreme conformations, and it can be seen that 10a, being the least sterically hindered, would be expected to be the most energetically



(10a)



(10b)



(10c)

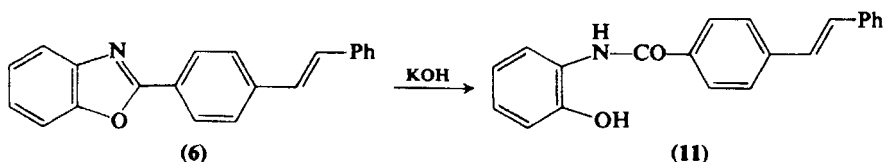
favorable. If it is assumed that elimination of the aniline molecule takes place by an E2 mechanism, the required *trans*-coplanar configuration of the groups being eliminated is only obtained in 10a and 10b. Elimination from 10b would lead to a *cis*-stilbene, whereas 10a leads to formation of the *trans* isomer.

E. SIDE REACTIONS

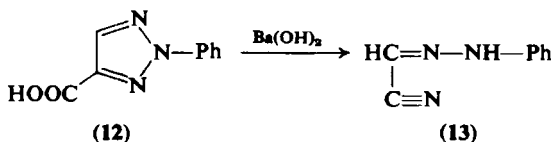
1. *Cleavage of the Heterocyclic Ring*

Because of the strongly basic conditions required for the Anil Synthesis, it is not surprising that, in certain cases, cleavage of the heterocyclic ring can occur. This is one of the reasons for reaction temperature and time being maintained as low as possible.

In the case of the 2-(stilben-4-yl)benzoxazole (6), ring opening to the hydroxylanilide (11) has been observed¹¹ at elevated temperature.



Further, in the case of the *v*-triazole (12), ring opening occurs¹³ under the influence of barium hydroxide to give the hydrazone (13).



The incorporation of the aniline formed during reaction into a heterocyclic nucleus, thus leading to the formation of a new heterocycle, has been observed in the oxadiazole¹¹ (see Section V) and coumarin¹⁴ (see Section XII,B) series.

2. *Oxidation Reactions*

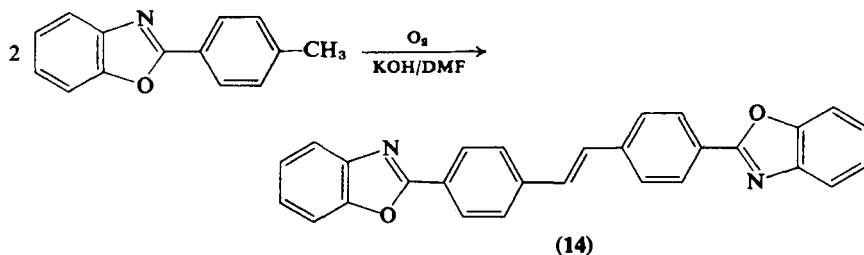
In the presence of air or oxygen, it has been shown¹⁵ that *p*-tolyl-substituted heterocycles in DMF with potassium hydroxide are oxidized to symmetrical stilbenes. Thus, for example, 2-(*p*-tolyl)benzoxazole yields 4,4'-bis(benzoxazol-2-yl)stilbene (14). Similar reactions have also been carried out with *p*-tolyl-substituted benzotriazoles, oxazoles, 1,3,4-thiadiazoles, 1,2,4- and 1,3,5-triazines, and quinazolines.

¹³ R. M. Carman, D. J. Brecknell, and H. C. Deeth, *Tetrahedron Lett.*, 4387 (1966); D. J. Brecknell, R. M. Carman, H. C. Deeth, and J. J. Kibby, *Aust. J. Chem.*, **22**, 1915 (1969).

¹⁴ O. S. Wolfbeis and E. Ziegler, *Z. Naturforsch. B* **31**, 514 (1976) and *B* **32**, 1496 (1977).

¹⁵ A. E. Siegrist, P. Liechti, E. Maeder, and L. Guglielmetti (Ciba-Geigy AG), *U.S. Patent* 3,546,217 (Swiss. Appl. 1965).

It is thus essential that the condensation of such compounds with Schiff's bases be carried out under an inert atmosphere.



In the case of compounds containing the azobenzene group, oxidation has been found to occur,¹⁶ yielding either symmetrical dibenzyls or stilbenes depending on the substitution of the azobenzene. It was, however, pointed out that this is a consequence of the oxidative ability of the azo group,¹⁷ since these reactions also take place under a nitrogen atmosphere.

A further oxidative reaction, in this case accompanied by rearrangement, has also been observed¹⁸ in the reaction of 4-benzylalkylamino-azobenzenes with Schiff's bases. Thus, reaction of the methyl-substituted azobenzene **15** with Schiff's base (**16**) gives at 40° to 45°C the expected stilbene **17**. However, at higher temperature this product undergoes oxidative rearrangement to the *N*-ethylketimine (**18**).

3. Reactions of Chlorine-Containing Compounds

In the triazolopyridine series it has been observed¹⁹ that a chloro substituent in an ortho position to the methyl group of tolyl heterocycles exerts an additional activating effect. Thus, in the case of triazolopyridine (**19**), reaction with Schiff's base from benzaldehyde and *p*-chloro-aniline yields the expected stilbene (**20**), whereas no reaction is observed in the case of the analog lacking the chlorine atom.

It is thus not surprising that a number of differing reactions have been observed in the case of chloro-substituted tolyl heterocycles.

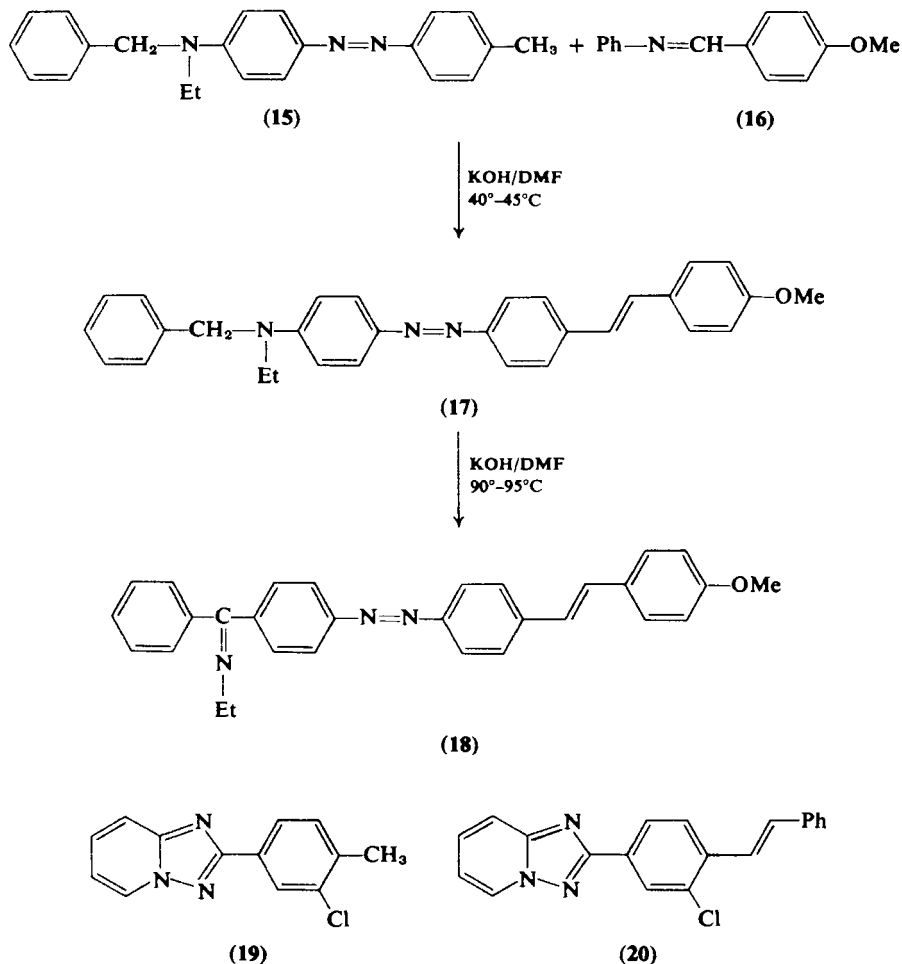
2-(3-Chloro-4-methylphenyl)benzotriazole (**21**) has thus been found to react with Schiff's base (**22**) to yield the 1,2,3-triarylpropane derivative

¹⁶ B. Weickhardt and A. E. Siegrist, *Helv. Chim. Acta* **55**, 138 (1972).

¹⁷ A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,819,615 (Swiss. Appl. 1971).

¹⁸ B. Weickhardt and A. E. Siegrist, *Helv. Chim. Acta* **55**, 173 (1972).

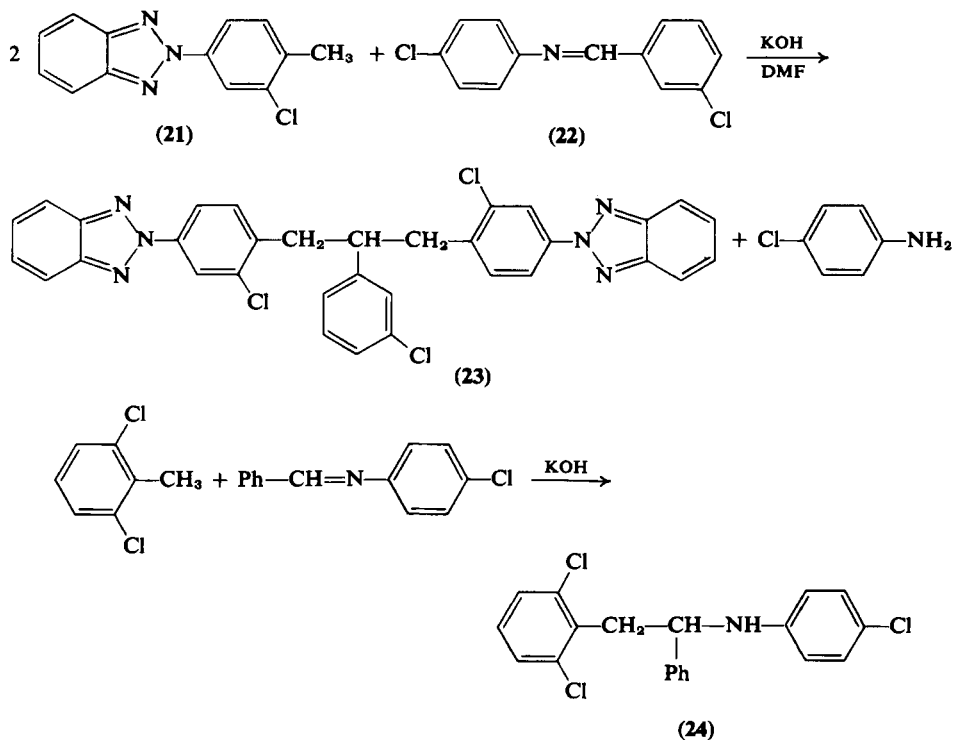
¹⁹ J. P. Pauchard and A. E. Siegrist, *Helv. Chim. Acta*, **61** 142 (1978).



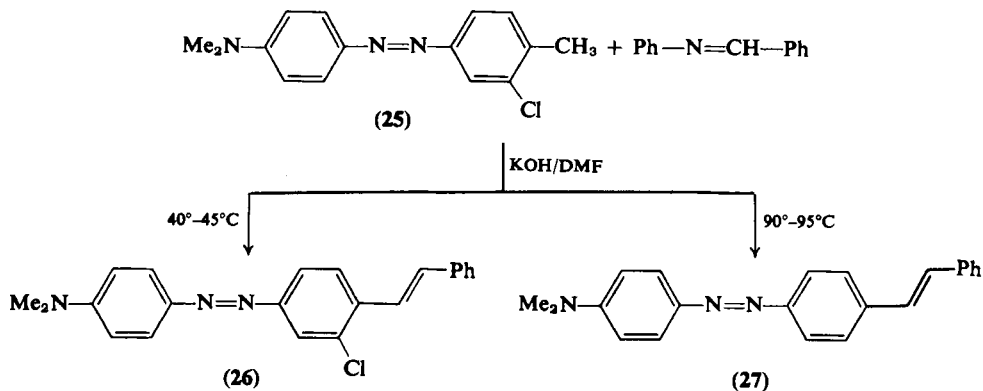
23.²⁰ Similar reaction was also observed with the corresponding 2H-naphtho[1,2-*d*]triazole, benzoxazole, and 4,5-diphenyloxazole.

An interesting variation in reactivity has also been shown²⁰ in the carbocyclic series on reaction of Schiff's base derived from aniline and *p*-chlorobenzaldehyde with a number of isomeric dichlorotoluenes. 2,4-Dichlorotoluene yields only the expected stilbene; 2,5-dichlorotoluene, according to reaction conditions and molar ratios, gives either the stilbene or 1,2,3-triarylpropane, whereas 2,6-dichlorotoluene yields only the addition product **24**.

²⁰ V. Coviello and A. E. Siegrist, *Helv. Chim. Acta* **59**, 802 (1976).



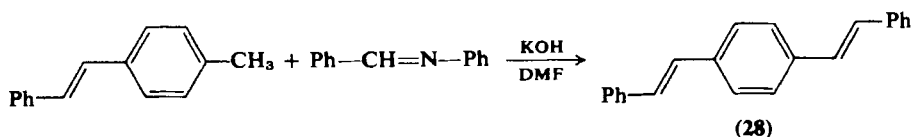
Finally, in the azobenzene series it has been found¹⁸ that during reaction, exchange of chlorine for hydrogen may occur above 60°C, as illustrated by the case of 3-chloro-4-methyl-4'-dimethylaminoazobenzene (25), which, depending on reaction temperature, reacts with benzaldehyde to yield either the expected stilbene (26) or its dechlorinated analog (27).



III. Carbocycles

When it was found by Becker⁸ that *p*-phenylsulfonylstilbene could readily be obtained by condensation of phenyl-*p*-tolylsulfone with benzalaniline, it was considered that this was a result of the stabilization of the *p*-tolyl anion by the mesomeric effect of the sulfone group.

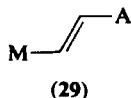
The electron-withdrawing effect of the C=N group in benzoxazoles, having long been known¹ to give rise to the acidity of 2-methylbenzoxazole, thus later^{10,11} led to the preparation of the benzoxazolystilbenes. Surprisingly, it was found^{21,22} that a conjugated system of carbon-carbon double bonds is sufficient to stabilize an anion and allow reaction with Schiff's bases in DMF in the presence of potassium hydroxide, *trans*-4-methylstilbene, for example, giving 1,4-distyrylbenzene (28).²¹



Apart from further stilbenes²³ containing sulfonic acid groups, reaction has also been observed with methyl-substituted tolans,^{21,24} bi- and terphenyls,^{21,22} naphthalenes,^{21,22,25} anthracenes,^{21,22} phenanthrenes,^{21,22} and even benzenes,^{21,22} whereby up to four methyl groups can be brought to react.

Table I shows the yields, melting points (°C), and UV absorption and fluorescence maxima (nanometers in DMF) of a number of styryl derivatives of carbocyclic compounds that have been prepared analogously from the aforementioned methyl compounds and a variety of Schiff's bases.

In Table I and in Tables II, V, VII, IX, X, XII, XVI, the general formula 29 represents the product resulting from condensation of a methyl component (M-CH₃) with a Schiff's base derived from an aldehyde (A-CHO) and an aniline.



²¹ A. E. Siegrist, P. Liechti, H. R. Meyer, and K. Weber, *Helv. Chim. Acta* **52**, 2521 (1969).

²² A. E. Siegrist, P. Liechti, H. R. Meyer, and K. Weber (Ciba-Geigy AG), U.S. Patent 3,991,049 (Swiss Appl. 1967).

²³ H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,522,679 (Swiss Appl. 1974).

²⁴ H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,525,680 (Swiss Appl. 1974).

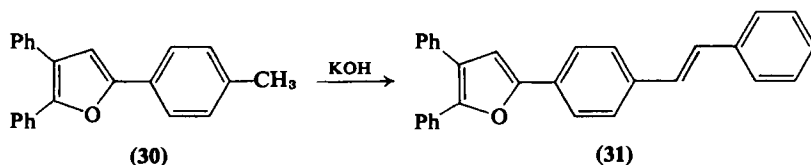
²⁵ R. H. Martin, M.-J. Marchant, and M. Baes, *Helv. Chim. Acta* **54**, 358 (1971).

This surprising reactivity of extremely weakly acidic methyl groups has resulted in extending the Anil Synthesis to a number of heterocyclic systems in which activation in the sense of the benzoxazole group would not be expected.

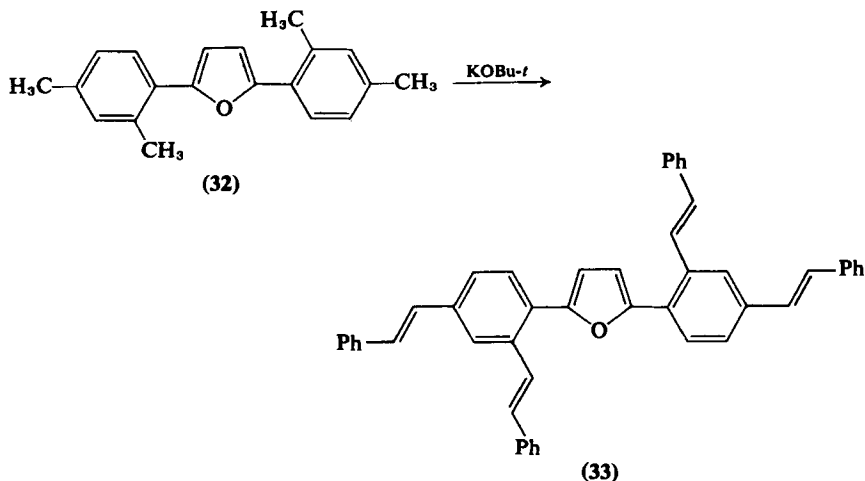
IV. Furans, Benzo[*b*]furans, Naphtho[*b*]furans, and Dibenzofurans

2,5-Diphenylfuran, 2-phenylbenzo[*b*]furan, and dibenzofuran have been found to be stable under the conditions of the Anil Synthesis. Hence, their methyl derivatives have been reacted with anils at higher temperatures, with the result that more than one methyl group within the same molecule is brought to react.

For example, reaction of 2,3-diphenyl-5-(*p*-tolyl)furan (30) with Schiff's base derived from benzaldehyde and *p*-chloroaniline in the presence of potassium hydroxide at 60°–65°C yields the stilbenylfuran 31.^{26,27} Moreover, at 90° to 95°C in the presence of potassium *t*-butoxide



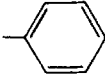
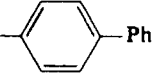
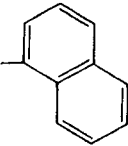
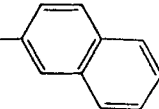
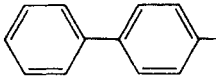
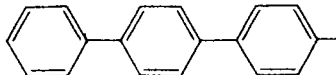
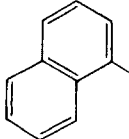
2,5-bis(2,4-dimethylphenyl)furan (32) forms 2,5-bis(2,4-distyrylphenyl)furan (33).²⁶

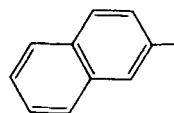
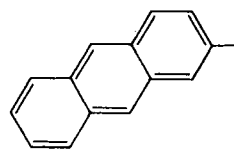
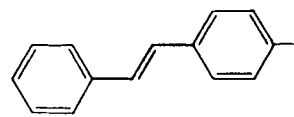
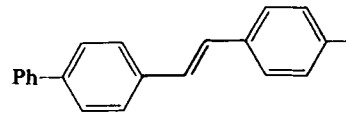
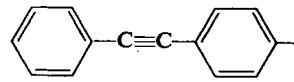
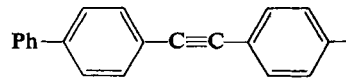


²⁶ A. E. Siegrist and H. R. Meyer, *Helv. Chim. Acta* 52, 1282 (1969).

²⁷ A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,697,513 (Swiss Appl. 1967).

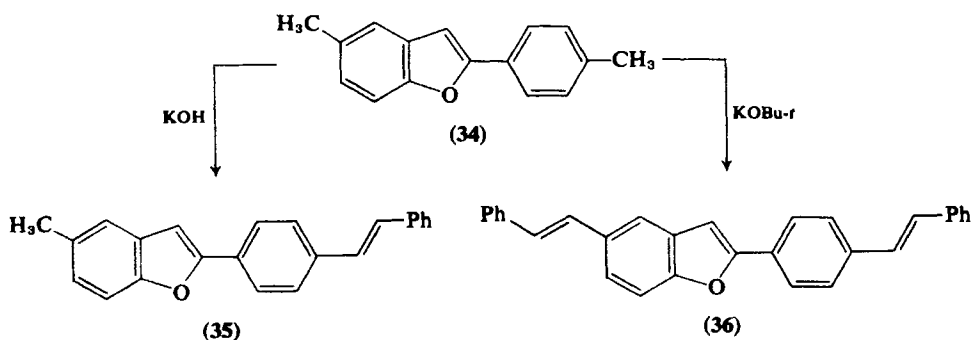
TABLE I
CARBOCYCLIC STYRYL DERIVATIVES^a

M	A			
				
	66% 222°–223°C 328/381 nm	18% 307°–308°C 345/407 nm	— — —	37% 231°–232°C 340/395 nm
	52% 315°–316°C 337/399 nm	53% 367°–368°C 349/419 nm	— — —	58% 312°–313°C 350/412 nm
	52% 71.5°–72°C 327/393 nm	25% 141°–142°C 342/— nm	51% 163°–164°C 346/427 nm	32% 189°–190°C 341/405 nm

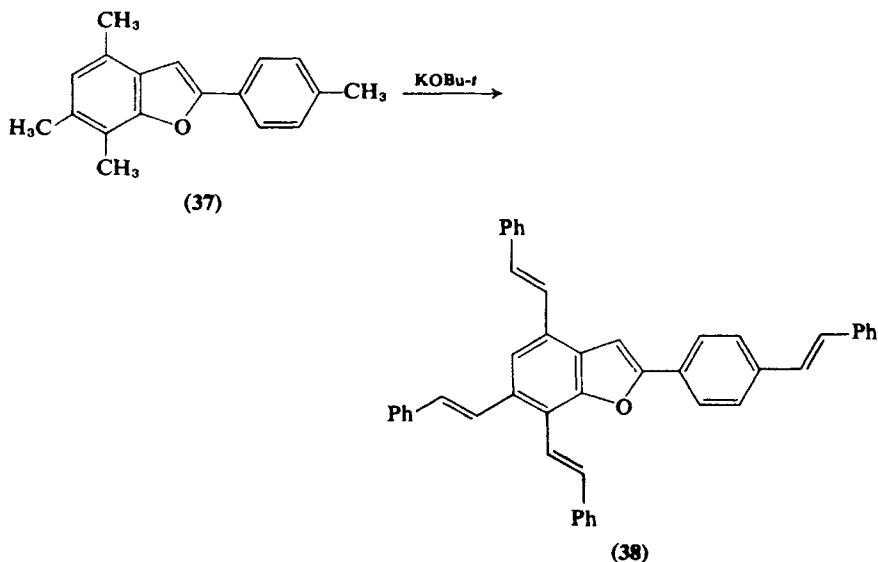
	67% 148°–149°C 320/381 nm	35% 231°–232°C 340/394 nm	74% 189°–190°C 340/405 nm	37% 259°–260°C 333/384 nm
	62% 256°–257°C 326/440 nm	48% 311°–312°C 340/449 nm	78% 225°–226°C 333/459 nm	58% 324°–325°C 334/447 nm
	84% 265°–266°C 357/413 nm	61% 318°–319°C 368/431 nm	69% 178°–179°C 365/435 nm	58% 266°–267°C 367/424 nm
	76% 317°–318°C 368/431 nm	77% 327°–373°C 380/446 nm	71% 247°–248°C 378/452 nm	77% 320°–321°C 378/442 nm
	67% 214°–215°C 343/391 nm	72% 276°–277°C 355/415 nm	62% 135°–136°C 353/426 nm	67% 224°–225°C 353/408 nm
	73% 269°–270°C 349/404 nm	80% 332°–333°C 363/424 nm	63% 218°–219°C 359/433 nm	80% 281°–282°C 360/417 nm

^a From Siegrist *et al.* (Ref. 21).

In the case of methyl-substituted 2-phenylbenzo[*b*]furans, the methyl groups show differing reactivity depending on the site to which they are attached. Thus, reaction of 2-(*p*-tolyl)-5-methylbenzo[*b*]furan (34) with Schiff's base from benzaldehyde and *p*-chloroaniline in the presence of potassium hydroxide yields 2-(stilben-4-yl)-5-methylbenzo[*b*]furan (35), whereas with potassium *t*-butoxide the 5-methyl group of the benzofuran ring also reacts, yielding the 5-styryl derivative 36.^{26,27}

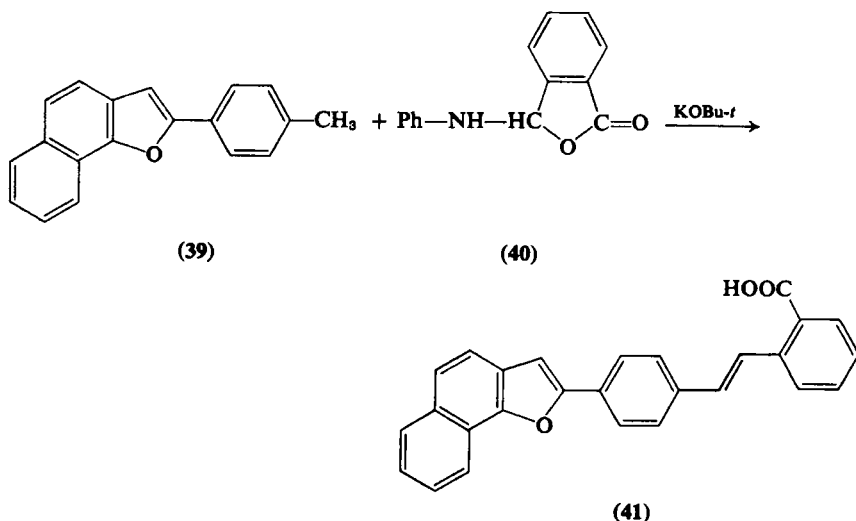


With potassium *t*-butoxide it has been shown²⁶ that up to four methyl groups in the same molecule can be brought to react, for example 2-(*p*-tolyl)-4,6,7-trimethylbenzo[*b*]furan (37) yields 2-(stilben-4-yl)-4,6,7-tristyrylbenzo[*b*]furan (38).



Such reactions have also been carried out on benzofurans carrying benzyl, fluoro, chloro, bromo, methoxy, cyano, and phenyl groups in the benzo ring. Substitution in the stilbene part of the molecule can also be obtained by the use of Schiff's bases derived from differing benzaldehydes.^{26,28,29}

Crounse and Desai²⁹ showed further that 2-(*p*-tolyl)benzo[*b*]furan with Schiff's base derived from terephthalaldehydic acid and aniline gives, on treatment with excess potassium *t*-butoxide, the corresponding stilbene carboxylic acid. Schiff's base derived from phthalaldehydic acid and aniline exists³⁰ as the 3-anilinophthalide (40). Nevertheless, this also reacts similarly with, for example, the naphthofuran (39) to form 2-(2'-carboxystilben-4-yl)naphtho[1,2-*b*]furan (41).²⁹ Analogous car-



boxylic acid amides and esters have been patented³¹ for use as fluorescent whitening agents.

Meyer³² has shown that 2-(stilben-4-yl)- and 7-styrylbenzo[*b*]furans containing sulfonic acid groups can be prepared from the phenyliminomethyl derivatives of benzene, biphenyl, and naphthalene.

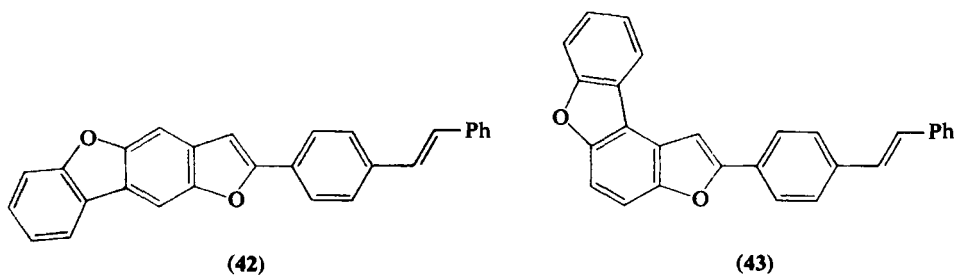
²⁸ N. N. Crounse and K. B. Desai (Sterling Drug Inc.), U.S. Patents 3,781,279 and 3,932,301 (U.S. Appl. 1971 and 1973).

²⁹ N. N. Crounse and K. B. Desai (Sterling Drug Inc.), U.S. Patent 3,833,510 (U.S. Appl. 1972).

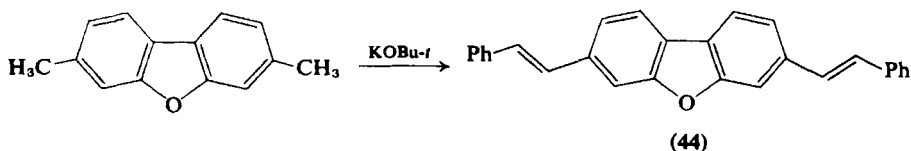
³⁰ Y. Kubota and T. Tatsuno, *Chem. Pharm. Bull.* **19**, 1226 (1971).

³¹ N. N. Crounse and K. B. Desai (Sterling Drug Inc.), U.S. Patent 3,974,144 (U.S. Appl. 1973).

Finally it has been found²⁸ that from a mixture of 2-(*p*-tolyl)benzofurano[3,2-*f*]- and [3,2-*e*]benzofuran, the two isomeric stilbene derivatives (42) and (43) can be obtained.

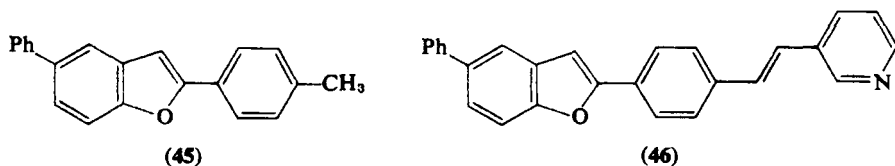


Reaction of 3,7-dimethyldibenzofuran with a number of benzaldehydes leads to the formation of the corresponding distyryldibenzofurans (44).^{26,27}



In Table II are compiled the results of a number of experiments with styryl and stilbenyl derivatives of furans and benzo[*b*]- and naphtho[*b*]furans.

Methyl-substituted 2-phenylbenzo[*b*]furans and dibenzofurans can also react with Schiff's bases derived from heteroaromatic aldehydes to yield styryl compounds, provided that these heterocycles are stable at the relatively high reaction temperatures required. Thus, for example, 2-(*p*-tolyl)-5-phenylbenzo[*b*]furan (45) with Schiff's base derived from 3-formylpyridine and *p*-chloroaniline in the presence of potassium hydroxide yields the vinylpyridine 46.^{33,34}



³² H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,525,683 (Swiss Appl. 1974).

³³ A. E. Siegrist and H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 1,965,654 (Swiss Appl. 1969).

³⁴ A. E. Siegrist and H. R. Meyer, *Helv. Chim. Acta*, in press.

The reverse process for the preparation of styryl derivatives of 2-phenylbenzo[*b*]furans and dibenzofurans by reaction of their phenyl-iminomethyl derivatives has led to the formation of a number of new styryl and stilbenyl compounds.³⁵⁻³⁷

Also, reaction of 2-phenyl-6-methylbenzo[*b*]furan with Schiff's base derived from 2-phenyl-6-formylbenzo[*b*]furan and *p*-chloroaniline (47) in the presence of potassium *t*-butoxide gives 1,2-di(2-phenylbenzo[*b*]furan-6-yl)ethylene (48).³⁷

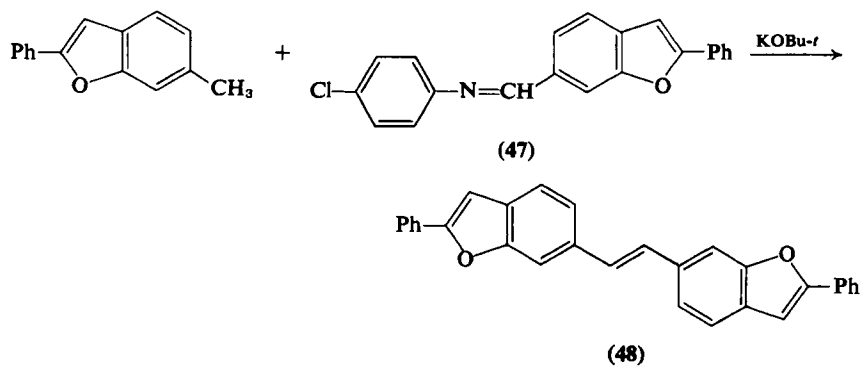
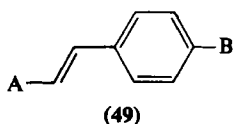


Table III shows a series of styryl compounds prepared from Schiff's bases of *p*-chloroaniline with 2- and 3-formyldibenzofuran, 2-(*p*-formylphenyl)benzo[*b*]furan, and 2-phenyl-6-formylbenzo[*b*]furan. (Further styryl derivatives from these anils are shown in Tables VI, VIII, XIV, and XVII.)

In Table III and in Tables IV, VI, VIII, XI, XIV, XV, the general formula 49 represents the product derived from condensation of a *p*-tolyl derivative (*p*-CH₃-C₆H₄-B) with a Schiff's base from an aldehyde (A-CHO) and an aniline.



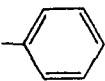
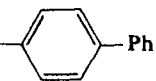
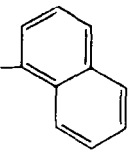
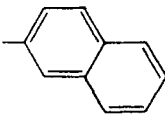
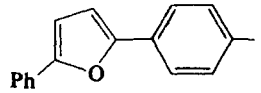
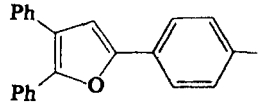
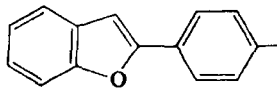
Furthermore, with the above-mentioned Schiff's bases, it is also possible to obtain compounds containing a single heterocyclic nucleus.

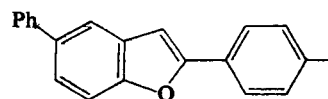
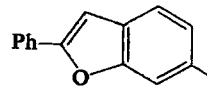
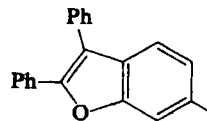
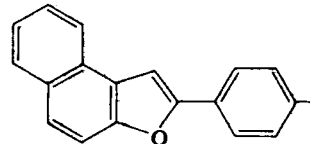
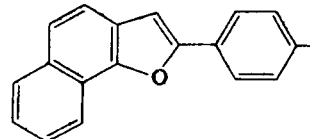
³⁵ A. E. Siegrist and J. Garmatter (Ciba-Geigy AG), U.S. Patent 3,796,707 (Swiss Appl. 1971).

³⁶ J. Garmatter and A. E. Siegrist, *Helv. Chim. Acta* **57**, 945 (1974).

³⁷ A. de Buman and A. E. Siegrist, *Helv. Chim. Acta* **57**, 1352 (1974).

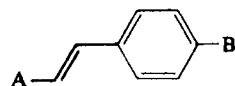
TABLE II
STYRYL DERIVATIVES OF FURANS AND CONDENSED FURANS^a

M	A			
				
	62% 205°–206°C 368/445 nm	70% 273°–274°C 380/463 nm	— — —	65% 256°–257°C 377/459 nm
	57% 188.5°C 370/446 nm	54% 261°–262°C 380/462 nm	— — —	— — —
	77% 271°–272°C 355/412 nm	61% 339°–340°C 368/428 nm	64% 182°–183°C 366/433 nm	80% 283°–284°C 366/421 nm

	74% 274°–275°C 359/413 nm	71% 357°–358°C 371/431 nm	78% 217°–218°C 368/439 nm	82% 287°–288°C 368/423 nm
	53% 196°–197°C 351/407 nm	24% 257°–258°C 365/426 nm	33% 145°–146°C 364/438 nm	28% 252°–253°C 361/420 nm
	23% 157°–158°C 352/411 nm	10% 233°–234°C 365/428 nm	— — —	13% 189°–190°C 361/422 nm
	78% 248°–249°C 370/438 nm	87% 316°–317°C 381/449 nm	74% 205°–206°C 380/457 nm	81% 296°–297°C 379/448 nm
	62% 225°–226°C 366/427 nm	64% 289°–290°C 377/443 nm	67% 228°–229°C 377/449 nm	62% 263°–264°C 375/437 nm

^a From Siegrist and Meyer (Ref. 26).

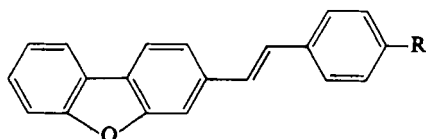
TABLE III
STYRYL DERIVATIVES OF BENZO- AND DIBENZOFURANS^a



A	B			
	62% 265°–266°C 358/418 nm	52% 250°–251°C 361/420 nm	— — —	47% 264°–265°C 360/418 nm
	56% 321°–322°C 373/432 nm	23% 331°–332°C 375/434 nm	54% 295°–296°C 384/453 nm	20% 339°–340°C 373/431 nm
	20% > 355°C 383/447 nm	20% > 355°C 388/448 nm	2% 353°–354°C 394/463 nm	5% > 355°C 382/447 nm
	63% 299°–300°C 381/445 nm	50% 285°–286°C 383/448 nm	57% 302°–304°C 410/457 nm	60% 313°–314°C 379/447 nm

^a Data from de Buman and Siegrist (Ref. 37) for benzofurans and from Garmatter and Siegrist (Ref. 36) for dibenzofurans.

Thus, for example,³⁶ reaction of Schiff's base from 3-formyldibenzofuran and *p*-chloroaniline with 4-methylstilbene and with 4-methyltolan in the presence of potassium hydroxide results in the formation of products **50** and **51**, respectively.



(50) $R = \text{CH}=\text{CH}-\text{Ph}$

(51) $R = \text{C}\equiv\text{C}-\text{Ph}$

The preparation of cyano-substituted styryl and stilbenyl compounds can be achieved^{38,39} by using sodium methoxide at room temperature. In this way, *o*-tolunitrile has been reacted with the anil of 2-(*p*-formylphenyl)benzo[*b*]furan and *p*-chloroaniline (**52**) to give 2-(2-cyano-stilben-4'-yl)benzo[*b*]furan (**53**).

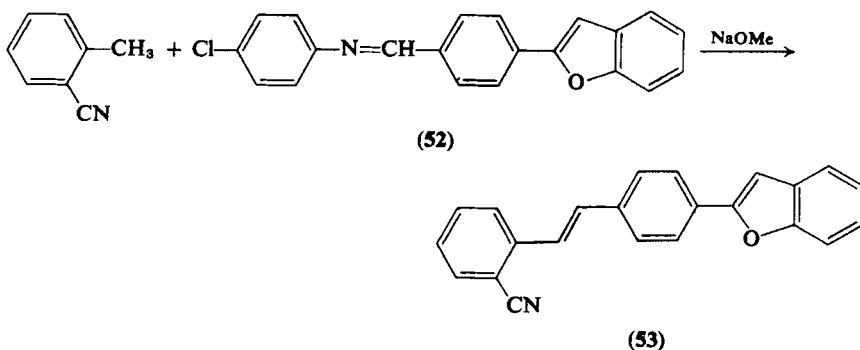


Table IV shows a further number of compounds that have been prepared from various tolunitriles.

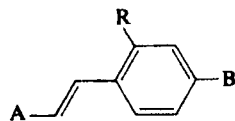
V. Oxazoles, Isoxazoles, and Oxadiazoles

Within this group of heterocycles, the greatest alkali stability, under the conditions of the Anil Synthesis, is exhibited by the 2,5-diaryloxazoles and the least by the 2,5-diaryl-1,3,4-oxadiazoles.

³⁶ A. E. Siegrist and V. Coviello (Ciba-Geigy AG), Ger. Offen. 2,453,355 (Swiss Appl. 1973).

³⁹ V. Coviello and A. E. Siegrist, *Helv. Chim. Acta* **59**, 819 (1976).

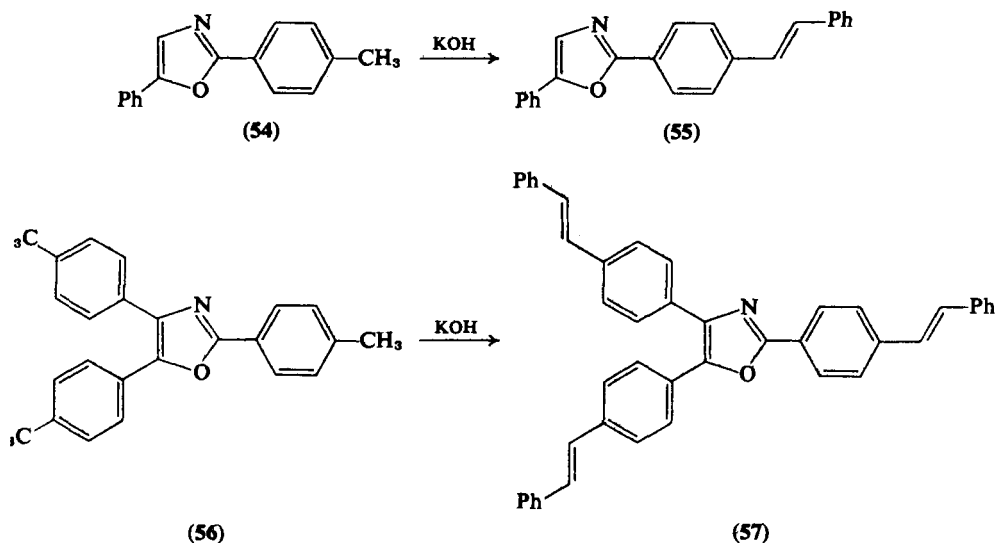
TABLE IV
CYANO-SUBSTITUTED DERIVATIVES^a



A	R: CN B: H	H CN	Cl CN	CH ₃ CN
	45% 143°–144°C 345 nm/—	65% 216°–217°C 350/421 nm	43% 214°–215°C 356 nm/—	18% 178°–179°C 350 nm/—
	61% 199°–200°C 363/455 nm	78% 268°–269°C 368/465 nm	56% 243°–244°C 369/497 nm	45% 232°–233°C 364/468 nm
	39% 164°–165°C 358/452 nm	83% 233°–234°C 365/467 nm	27% 193°–194°C 372/489 nm	— — —

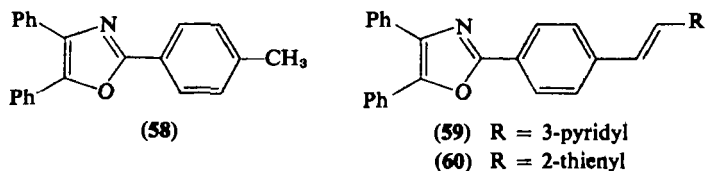
^a From Coviello and Siegrist (Ref. 39).

5-Phenyl-2-(*p*-tolyl)oxazole (54) reacts with benzaldehyde in the presence of potassium hydroxide to yield 5-phenyl-2-(stilben-4-yl)-oxazole (55), and the 2,4,5-tri(*p*-tolyl)oxazole (56) reacts with 3 moles of benzaldehyde to give the 2,4,5-tri(stilben-4-yl)oxazole (57).¹¹ Some



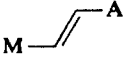
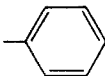
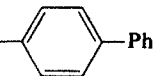
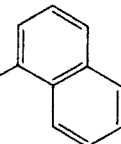
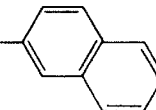
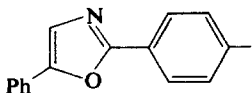
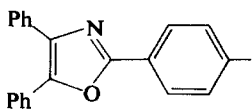
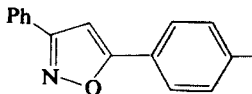
further stilbenyloxazoles that have been obtained analogously are illustrated in Table V.

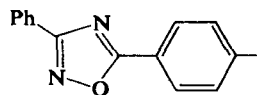
Besides benzaldehydes, also anils derived from heterocyclic aldehydes may be employed (Table VI), as, for example, in the reactions of 4,5-diphenyl-2-(*p*-tolyl)oxazole (58) with Schiff's bases from *p*-chloroaniline and 3-formylpyridine and 2-formylthiophene, leading, respectively, to the β -(3-pyridyl)-4-(4,5-diphenyloxazol-2-yl)styrene (59)³³ and the β -(2-thienyl) analog (60).¹¹



3,5-Di(*p*-tolyl)isoxazole (61) is also sufficiently stable to alkali to be subjected to the Anil Synthesis. Thus, with benzaldehyde in the presence of potassium hydroxide, the expected 3,5-di(stilben-4-yl)isoxazole (62) is formed.

TABLE V
STILBENYL DERIVATIVES OF OXAZOLES, ISOXAZOLES, AND OXADIAZOLES^a

M	A			
				
				
	25% 156°–157°C 358/420 nm	51% 230°–231°C 370/432 nm	7% 169°–170°C 366/441 nm	63% 214°–215°C 368/428 nm
	61% 181°–182°C 357/434 nm	79% 255°–256°C 369/440 nm	32% 159°–160°C 366/445 nm	65% 202°–203°C 368/437 nm
	23% 210°–211°C 339/390 nm	48% 300°–301°C 353/418 nm	— — —	— — —



12%
144°–145°C
338/414 nm

31%
230°–231°C
354/444 nm

—

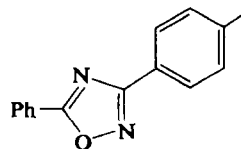
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28%
159°–160°C
328/388 nm

45%
228°–229°C
346/414 nm

—

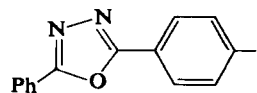
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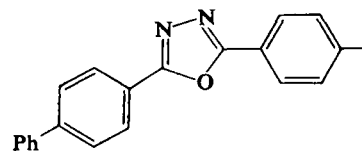


17%
168°–169°C
343/404 nm

29%
217°–218°C
357/430 nm

21%
188°–189°C
353/445 nm

17%
201°–202°C
354/428 nm



40%
227°–228°C
348/407 nm

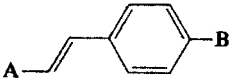
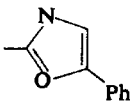
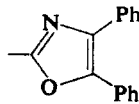
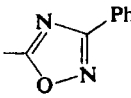
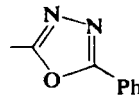
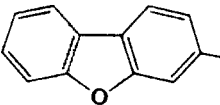
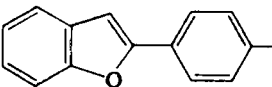
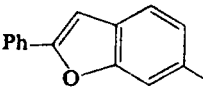
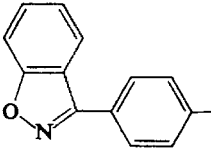
74%
286°–287°C
360/434 nm

21%
218°–219°C
356/447 nm

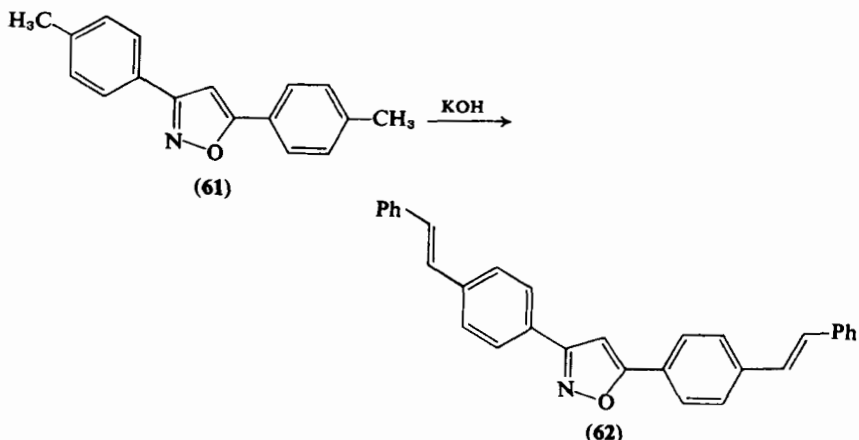
46%
265°–266°C
357/429 nm

^a From Siegrist (Ref. 11).

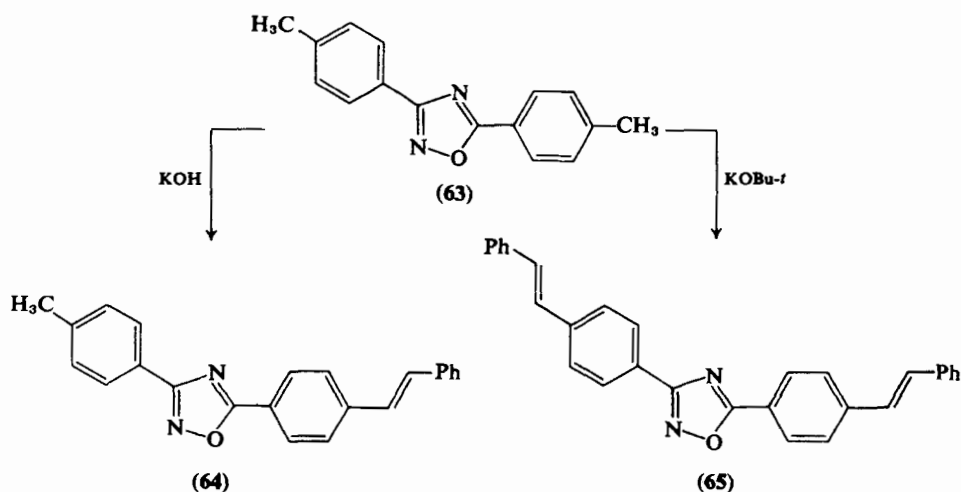
TABLE VI
STYRYL DERIVATIVES OF OXAZOLES AND OXADIAZOLES^a

A	B			
				
				
	19% 231°–232°C 373/436 nm	74% 239°–240°C 374/442 nm	83% 228°–229°C 359/448 nm	64% 246°–247°C 362/431 nm
	16% 267°–268°C 384/450 nm	8% 287°–288°C 386/453 nm	55% 269°–270°C 376/487 nm	68% 274°–275°C 375/465 nm
	71% 238°–239°C 384/454 nm	80% 235°–236°C 384/455 nm	61% 208°–209°C 375/492 nm	52% 241°–242°C 374/473 nm
	22% 190°–191°C 367/452 nm	27% 204°–205°C 367/464 nm	76% 216°–217°C 348/413 nm	39% 234°–235°C 352/410 nm

^a Data from Siegrist and co-workers (Refs. 36, 37, and 54).



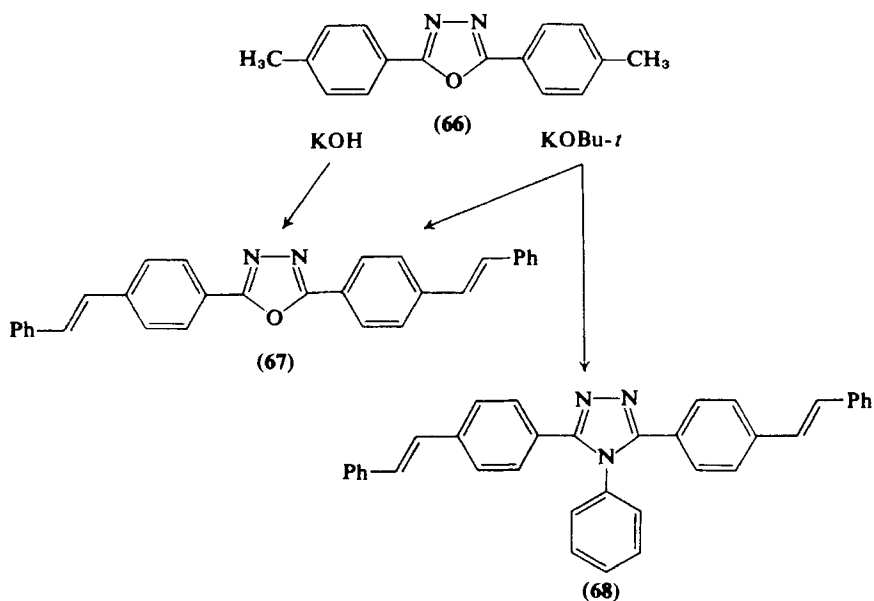
As was found in the case of the methyl-substituted 2-phenylbenzo-[b]furans (cf. 34), a similar variation in the reactivity of the methyl groups in 3,5-di(*p*-tolyl)-1,2,4-oxadiazole (63) has also been observed.¹¹ With benzalaniline in the presence of potassium hydroxide the 5-(stilben-4-yl)-3-(*p*-tolyl)-1,2,4-oxadiazole (64) is formed, whereas with potassium *t*-butoxide both methyl groups react, leading to 3,5-di(stilben-4-yl)-1,2,4-oxadiazole (65). Some further stilbene derivatives of 1,2,4-oxadiazoles are shown in Table V.



2,5-Di(stilben-4-yl)-1,3,4-oxadiazoles have been recognized as being useful fluorescent whitening agents.⁴⁰ They can be readily obtained from

⁴⁰ A. E. Siegrist, P. Liechti, E. Maeder, and L. Guglielmetti (Ciba-Geigy AG), U.S. Patent 2,642,783 (Swiss Appl. 1965).

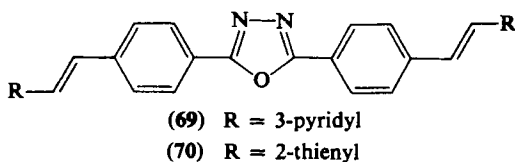
2,5-di(*p*-tolyl)-1,3,4-oxadiazole (**66**) and benzalaniline by the Anil Synthesis, whereby the aldehydic part of Schiff's base may be substituted with chloro, methoxy, or phenyl groups.⁴¹ Further substitution of this latter phenyl group by a sulfonic acid has also been reported.⁴¹ Thus, for example, compound **66** with benzalaniline and potassium hydroxide gives 2,5-di(stilben-4-yl)-1,3,4-oxadiazole (**67**). However, when potassium *t*-butoxide is employed as the base, a mixture consisting of **67** and the 3,5-di(stilben-4-yl)-4-phenyl-1,2,4-triazole (**68**) is obtained, as a result of incorporation of the aniline formed during reaction into the heterocyclic ring, a reaction of known⁴² type.



Apart from the anils derived from carbocyclic aldehydes, those from heteroaromatic aldehydes can also react with **66**. Schiff's bases obtained from *p*-chloroaniline and 3-formylpyridine and 2-formylthiophene thus yield products **69** and **70**, respectively. Table V shows some further stilbenyl-1,3,4-oxadiazoles that have been obtained from the *p*-tolyl-1,3,4-oxadiazoles and Schiff's bases by treatment with potassium hydroxide.

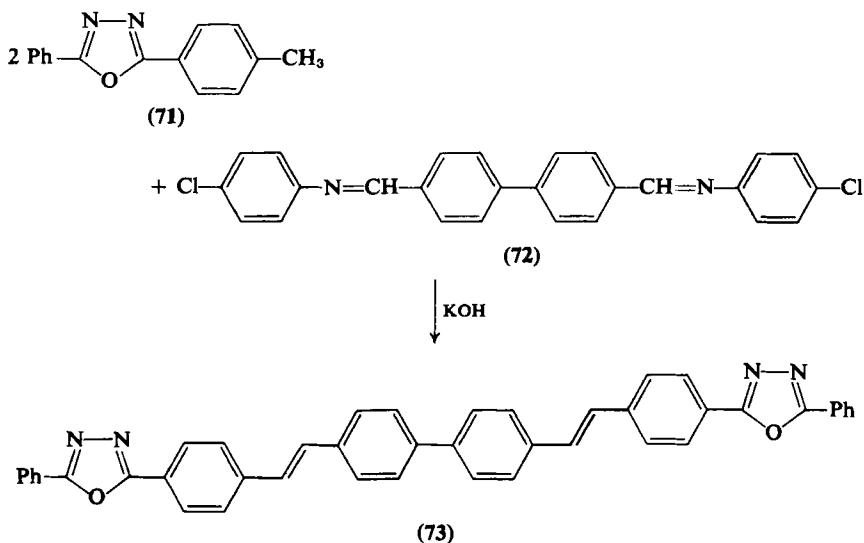
⁴¹ H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,525,637 (Swiss Appl. 1974).

⁴² Y. A. Levin and M. S. Skorobogotova, *Chem. Heterocycl. Compds.* 3, 266 (1967) [CA 67, 100076 (1967)].



In Tables VI, XI, XV, and XVII are compiled a number of styryl derivatives of oxazoles and oxadiazoles that have been prepared from Schiff's bases of heteroaromatic aldehydes.

Finally, dianils of aromatic dialdehydes may react with 2 moles of a *p*-tolyl-substituted heterocycle. For example, 5-phenyl-2-(*p*-tolyl)-1,3,4-oxadiazole (71) reacts with Schiff's base from 2 moles of *p*-chloroaniline and 4,4'-diformylbiphenyl (72) to give 4,4'-bis[4-(5-phenyl-1,3,4-oxadiazol-2-yl)styryl]biphenyl (73).⁴³ Along with further *p*-tolyl-substituted heteroaromatics, a number of carbocyclic aromatics have



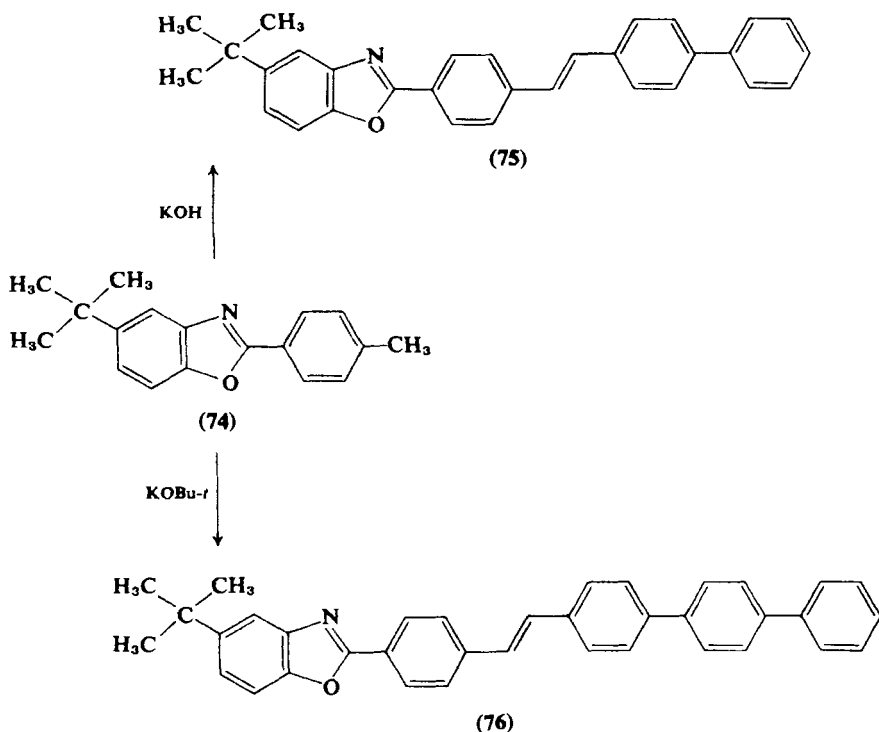
also been reacted in this way.^{39,43,44} However, as a result of their better solubility, the Schiff's bases derived from aromatic dialdehydes and *o*-chloroaniline were found to be preferable.^{39,44}

⁴³ A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,830,848 (Swiss Appl. 1970).

⁴⁴ V. Coviello and A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,453,357 (Swiss Appl. 1973).

VI. Benzoxazoles, Naphthoxazoles, and Benzisoxazoles

The benzoxazole system has been found^{2,3} to be an important building block for a number of light-stable fluorescent whitening agents, especially for use on polyester fibers. The technically interesting 2-(4-phenylstilben-4'-yl)benzoxazoles⁴⁵⁻⁴⁷ have been found to be obtained via the Anil Synthesis.^{10,11} Thus, reaction of 2-(*p*-tolyl)-5-*t*-butylbenzoxazole (74) with Schiff's base from 4-formylbiphenyl and aniline in the presence of potassium hydroxide leads to 2-(4-phenylstilben-4'-yl)-5-*t*-butylbenzoxazole (75).⁴⁵ Similarly, with the corresponding anil from 4-formyl-*p*-terphenyl under the influence of potassium *t*-butoxide, compound 76 is obtained.⁴⁸



⁴⁵ A. E. Siegrist, P. Liechti, E. Mader, and H. R. Meyer (Ciba-Geigy AG), U.S. Patent 3,781,278 (Swiss Appl. 1965 and 1966).

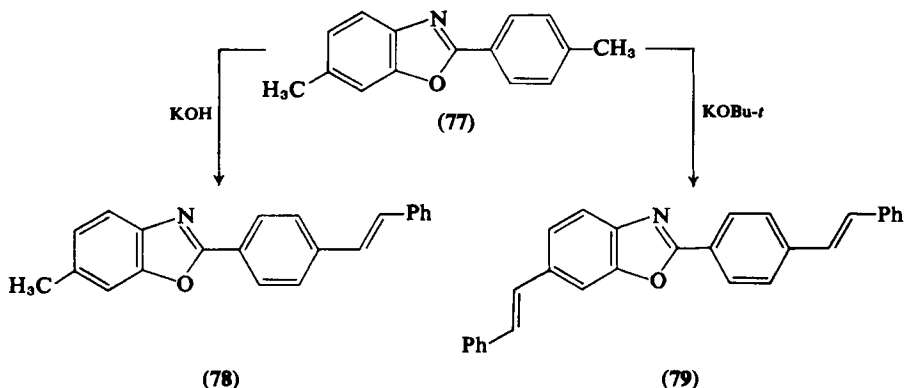
⁴⁶ F. Fleck and S. Valenti (Sandoz AG), Ger. Offen. 2,028,037 (Swiss Appl. 1969).

⁴⁷ C. Luethi (Ciba-Geigy AG), U.S. Patent 3,850,914 (Swiss Appl. 1971).

⁴⁸ F. Fleck, H. Kittl, and S. Valenti (Sandoz AG), Ger. Offen. 2,262,340 (Swiss Appl. 1971).

Similar reaction has also been carried out with benzoxazoles substituted in the benzo ring with up to three substituents, such as chloro, alkyl, alkoxy,⁴⁸ phenoxy,⁴⁹ phenyl, cycloalkyl, or sulfamoyl¹⁰ groups. By employing anils of substituted aromatic aldehydes, varying groups may also be introduced into the stilbene part of the molecule.⁵⁰ Water-soluble derivatives have also been obtained by the use of sulfonic acid-substituted *p*-tolylbenzoxazoles and also aromatic aldehyde anils.⁵¹

As previously mentioned, the benzoxazole ring system is sensitive to alkali at higher temperatures. Furthermore, methyl groups in differing positions on the benzo ring exhibit varying reactivity. As opposed to the benzo[*b*]furan series in which methyl groups in all four positions of the benzo ring have been found to react,²⁶ with the corresponding benzoxazole derivatives, only the 6-methyl group has been found capable of condensation.¹¹ Thus, in the reaction of 2-(*p*-tolyl)-6-methylbenzoxazole (77) with benzalaniline, use of potassium hydroxide as base leads only to the formation of the 2-(stilben-4-yl)-6-methylbenzoxazole (78), whereas potassium *t*-butoxide results in the formation of the 6-styryl analog 79; methyl groups in other positions fail to react.¹¹



2-Aryl-6-styrylbenzoxazoles have also been found to be useful fluorescent whitening agents.⁵² Further styryl and stilbenyl derivatives are shown in Table VII.

Compounds of high molecular weight can also be reacted, provided that they are sufficiently soluble in DMF. Thus, 2,2'-di-(*p*-tolyl)-6,6'-bis-

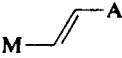
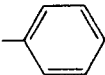
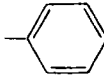
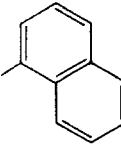
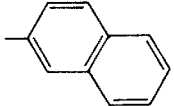
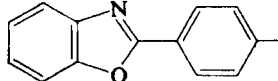
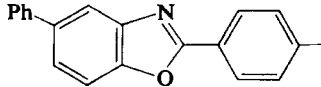
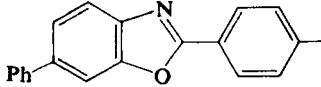
⁴⁸ P. Liechti (Ciba-Geigy AG), Ger. Offen. 2,306,050 (Swiss Appl. 1972).

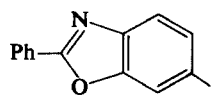
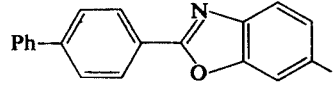
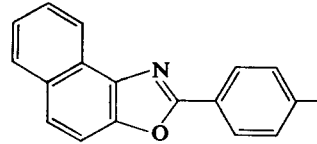
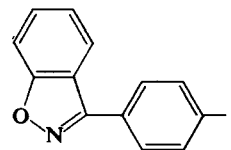
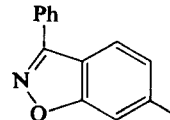
⁵⁰ D. Guenther, H. Nestler, G. Roesch, E. Schinzel, and R. Erckel (Hoechst AG), Ger. Offen. 2,540,236 (Swiss Appl. 1974).

⁵¹ H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,525,681 and 2,525,684 (Swiss Appl. 1974).

⁵² P. Liechti, E. Maeder, and A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,711,472 (Swiss Appl. 1965 and 1966).

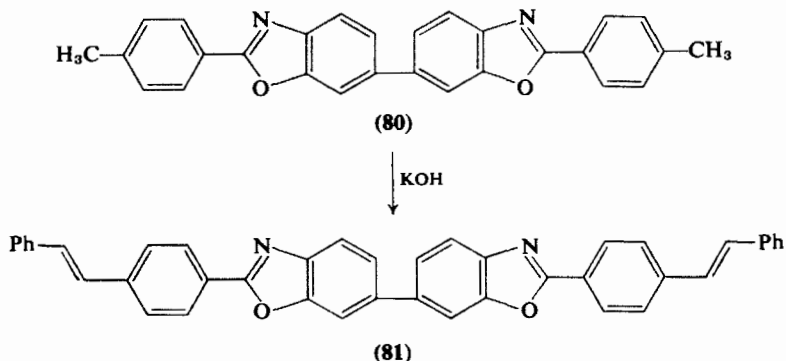
TABLE VII
STYRYL DERIVATIVES OF BENZOXAZOLES AND BENZISOXAZOLES^a

M	A			
				
				
	18% 199°–200°C 350/403 nm	45% 276°–277°C 362/431 nm	13% 165°–166°C 359/448 nm	6% 225°–226°C 360/428 nm
	26% 236°–237°C 356/409 nm	60% 294°–295°C 367/437 nm	7% 150°–151°C 363/450 nm	31% 261°–262°C 364/429 nm
	8% 225°–226°C 360/422 nm	61% 284°–285°C 370/440 nm	9% 183°–184°C 366/450 nm	19% 264°–265°C 370/434 nm

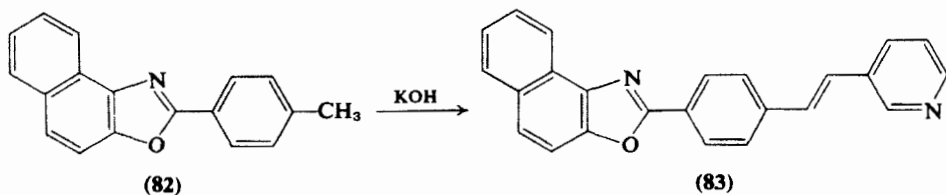
	10% 146°–147°C 344/423 nm	12% 215°–216°C 357/430 nm	— — —	— — —
	13% 203°–204°C 355/447 nm	4% 289°–290°C 365/456 nm	— — —	15% 248°–249°C 365/456 nm
	38% 204°–205°C 369/427 nm	64% 259°–260°C 377/440 nm	17% 206°–207°C 375/448 nm	40% 256°–257°C 377/436 nm
	35% 174°–175°C 327/392 nm	51% 230°–231°C 343/417 nm	35% 105°–106°C 343/429 nm	52% 171°–172°C 337/412 nm
	56% 137°–138°C 324/385 nm	78% 207°–208°C 342/414 nm	47% 140°–141°C 342/427 nm	63% 181°–182°C 337/410 nm

^a Data from Siegrist (Ref. 11) for benzoxazoles and from de Sousa and Siegrist (Ref. 54) for benzisoxazoles.

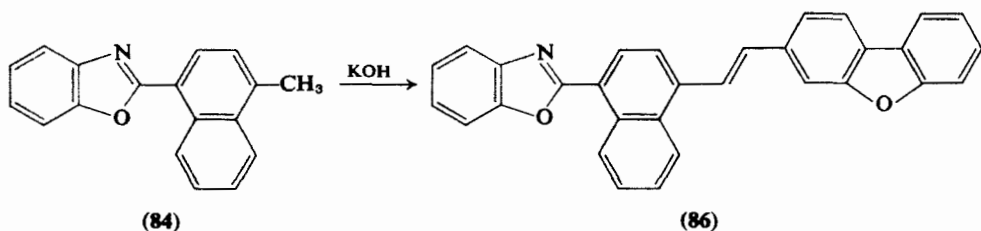
benzoxazole (80) gives, with benzalaniline and potassium hydroxide, the 2,2'-distilbenyl derivative 81.¹¹

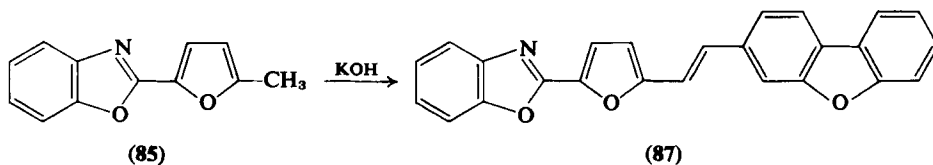


2-(*p*-Tolyl)benzoxazole and 2-(*p*-tolyl)naphthoxazole have also been found to undergo reaction with heteroaromatic aldehyde anils, as, for example, 2-(*p*-tolyl)naphth[1,2-*d*]oxazole (82), which, with Schiff's base from *p*-chloroaniline and 3-formylpyridine, yields the pyridylstyrene 83.³³ The 2-(*p*-tolyl) substituent in such compounds may be replaced

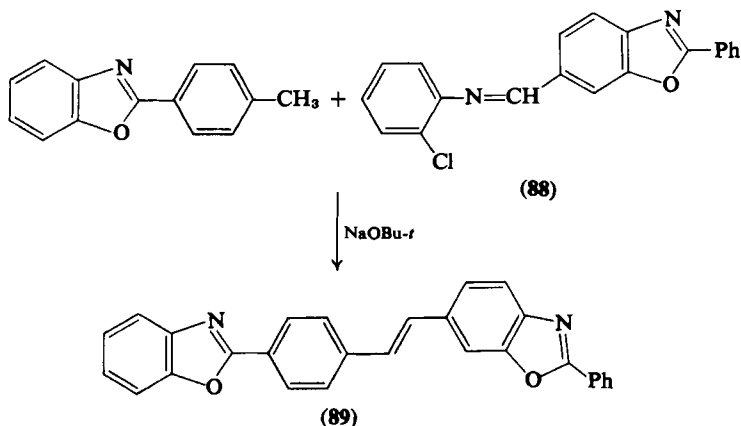


either by the 2-(4-methyl-1-naphthyl)- or 2-(5-methyl-2-furyl) groups. Thus, Schiff's base from 3-formyldibenzofuran and *p*-chloroaniline yields, when treated with 84 or 85, products 86 and 87, respectively.³⁶



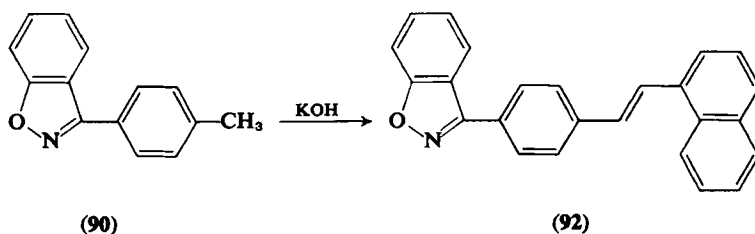


Finally, it has recently been shown that 2-(*p*-tolyl)benzoxazole reacts with Schiff's base (88) under the influence of sodium *t*-butoxide, giving β -(2-phenylbenzoxazol-6-yl)-4-(benzoxazol-2-yl)styrene (89).⁵³



A further series of styryl derivatives from benzoxazoles and heteroaromatic aldehyde anils are shown in Tables VIII, XI, XV, and XVII.

It has also been found recently that the 3-(*p*-tolyl)- and 3-phenyl-6-methyl-1,2-benzisoxazoles (90 and 91) can be utilized in the Anil Synthesis,⁵⁴ since this ring system was found to be alkali stable. Hence, for example, 90 and 91 give, on reaction with Schiff's base from 1-formylnaphthalene and *p*-chloroaniline, the styryl derivatives 92 and 93, respectively.



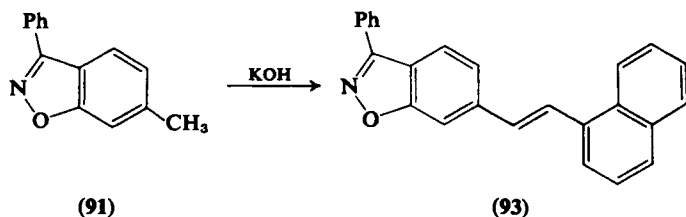
⁵³ G. Kormany (Ciba-Geigy AG), Ger. Offen. 2,756,408 (Lux. Appl. 1976).

⁵⁴ B. de Sousa and A. E. Siegrist, *Helv. Chim. Acta*, in press.

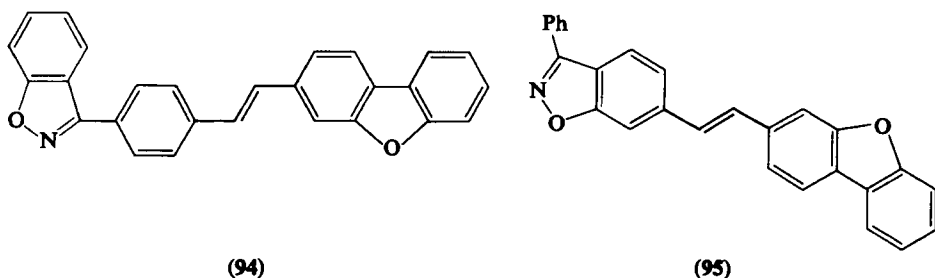
TABLE VIII: HETEROCYCLIC STYRYL DERIVATIVES OF BENZOXAZOLES AND BENZISOXAZOLES^a

A	B			
	54% 228°–229°C 355/433 nm	37% 225°–226°C 359/438 nm	67% 262°–263°C 367/442 nm	— — —
	70% 269°–270°C 368/436 nm	76% 279°–280°C 372/441 nm	74% 285°–286°C 375/442 nm	44% 213°–214°C 352/417 nm
	39% 342°–343°C 379/471 nm	21% 339°–340°C 384/473 nm	25% 328°–329°C 387/473 nm	— — —
	54% 259°–260°C 376/476 nm	63% 277°–278°C 382/484 nm	63% 285°–286°C 385/487 nm	61% 206°–207°C 365/455 nm
	44% 257°–258°C 360/417 nm	47% 255°–256°C 364/422 nm	50% 257°–258°C 368/433 nm	6% 243°–244°C 342/400 nm

^a Data from Siegrist and co-workers (Ref. 36, 37, and 54).



Further styryl and stilbenyl derivatives from **90** and **91** are shown in Table VII. Also reaction of these two compounds with heteroaromatic anils, such as that derived from 3-formyldibenzofuran and *p*-chloroaniline, leads to the formation of the styryl and ethylene compounds **94** and **95**, respectively.⁵⁴



In the case of the reaction of 3-(3-chloro-4-methylphenyl)-6-chloro-1,2-benzisoxazole (**96**), an enhanced reactivity of the methyl groups as opposed to the analog lacking the chlorine atoms (**90**) has been observed. Thus, with Schiff's base (**88**) from 2-phenyl-6-formylbenzoxazole and *o*-chloroaniline, compound **96** yields the styryl derivative **97**, whereas **90** fails to react under these conditions.⁵⁴

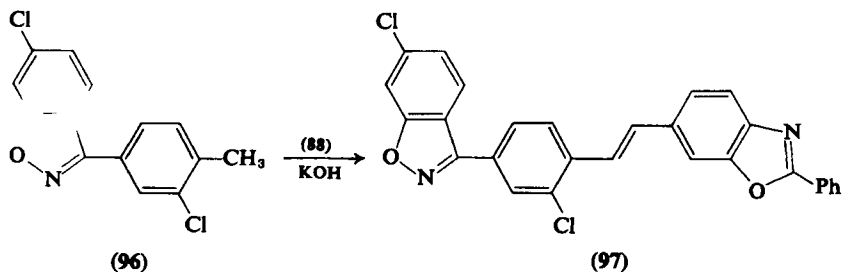
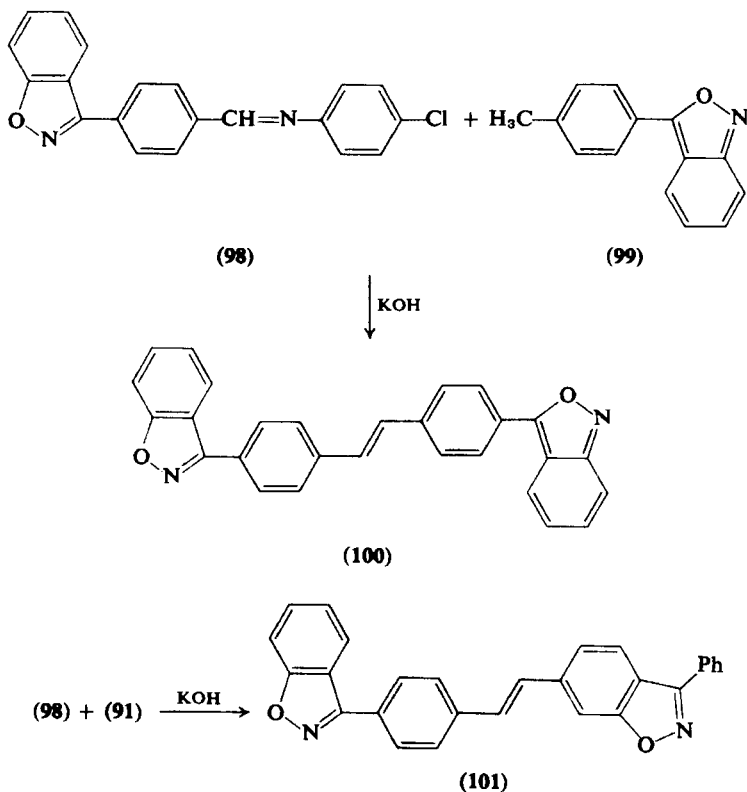


Table XVII illustrates a number of similar examples of the formation of chlorostyryl derivatives.

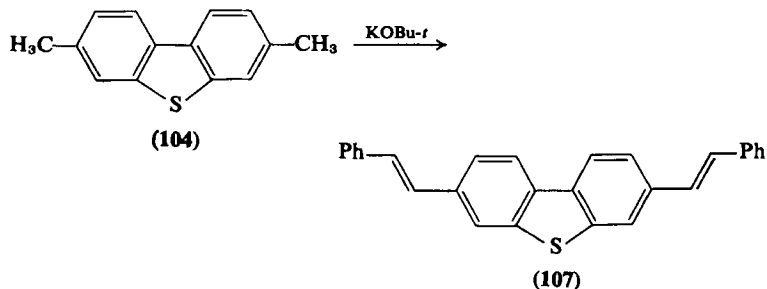
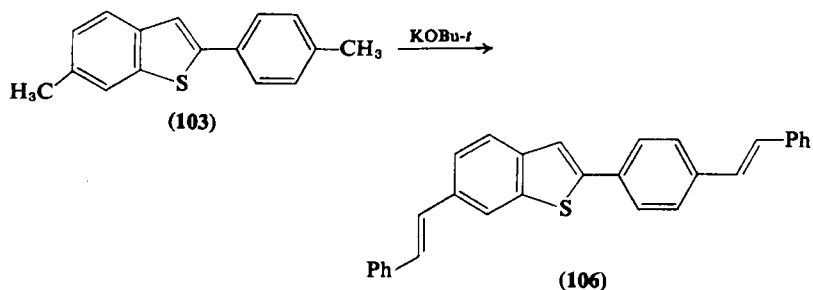
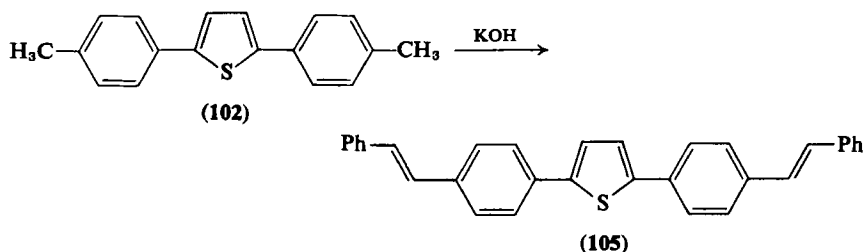
From Schiff's base **98**, by reaction with various *p*-tolyl-substituted heterocycles, a further series of styryl derivatives have been obtained (see Tables VI, VIII, and XVIII). For example, with 3-(*p*-tolyl)-2,1-benzisoxazole (**99**), the anil **98** yields the styryl compound **100**, and with **91**, compound **101**.⁵⁴



VII. Sulfur-Containing Heterocycles

A. THIOPHENES, BENZO[*b*]-, NAPHTHO[2,1-*b*]-, AND DIBENZOTHIOPHENES

2,5-Di(*p*-tolyl)thiophene (**102**), 2-(*p*-tolyl)-6-methylbenzo[*b*]thiophene (**103**), and 3,7-dimethyldibenzothiophene (**104**) are stable to alkali under the conditions of the Anil Synthesis. Thus, they may be reacted with 2 moles of benzalaniline to yield the distyryl compounds **105**, **106**, and **107**.^{26,27}



2-(*p*-Tolyl)-6-methylbenzo[*b*]thiophene (103) exhibits differing reactivity of the methyl groups in a similar manner to the corresponding benzo[*b*]furan (34), yielding,²⁶ with benzalaniline, under the influence of potassium hydroxide, just the 2-(stilben-4-yl)-6-methylbenzo[*b*]thiophene (108) [cf. 103 → 106 above].

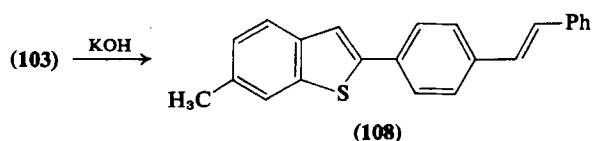
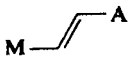
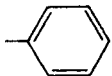
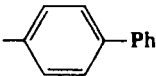
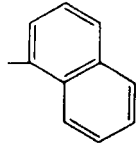
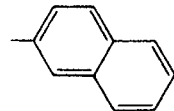
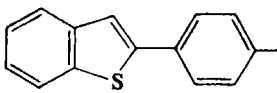
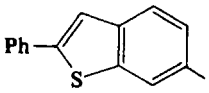
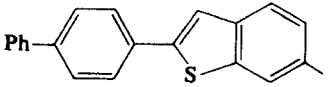
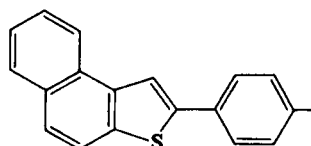
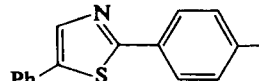
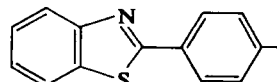
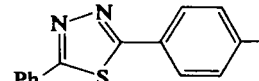


Table IX lists a number of styryl and stilbenyl derivatives of benzo[*b*] and naphtho[2,1-*b*]thiophenes.

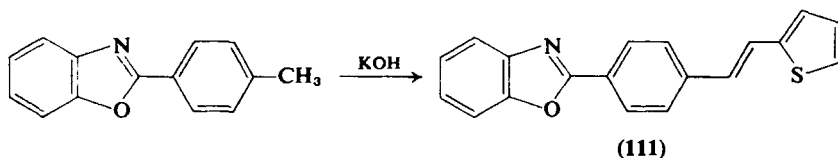
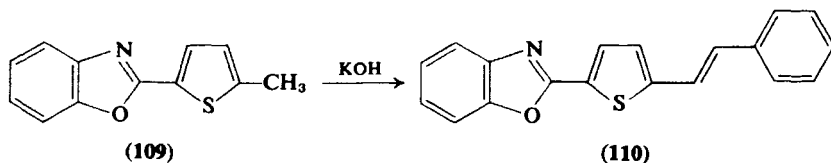
TABLE IX
STYRYL DERIVATIVES OF SULFUR-CONTAINING HETEROCYCLES

M	A			
				
				
	56% 294°–295°C 355/409 nm	49% 353°–354°C 367/427 nm	49% 206°–207°C 363/436 nm	62% 308°–309°C 365/420 nm
	46% 243°–244°C 354/408 nm	34% 297°–298°C 367/427 nm	36% 187°–188°C 365/437 nm	21% 293°–294°C 365/420 nm
	79% 311°–312°C 366/427 nm	— — —	45% 280°–281°C 373/438 nm	— — —

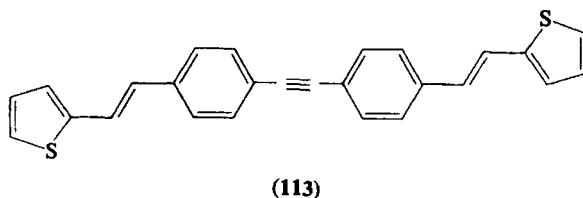
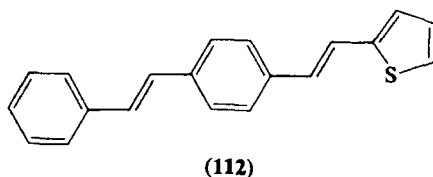
	80% 238°–239°C 370/428 nm	84% 302°–303°C 381/443 nm	65% 224°–225°C 380/449 nm	77% 284°–285°C 379/438 nm
	47% 210°–211°C 369/435 nm	50% 279°–281°C 380/447 nm	— — —	— — —
	34% 231°–232°C 357/415 nm	66% 299°–300°C 367/446 nm	26% 145°–146°C 365/458 nm	41% 249°–250°C 367/441 nm
	62% 227°C 357/445 nm	70% 320°–321°C 367/463 nm	— — —	— — —

^a From Siegrist (Ref. 11) and Siegrist and Meyer (Ref. 26).

2-Methyl-substituted thiophenes are also capable of reaction with benzalaniline, provided that the 5-position carries a carbo- or heterocyclic aromatic group, as, for example, 2-(benzoxazol-2-yl)-5-methylthiophene (**109**), which yields the styryl derivative **110**.¹¹ The isomeric compound **111** may be obtained analogously from 2-(*p*-tolyl)benzoxazole and Schiff's base from 2-formylthiophene and *p*-chloroaniline.

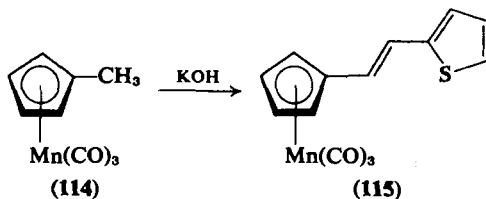


This latter Schiff's base, in the presence of potassium hydroxide and with 4-methylstilbene and with 4,4'-dimethyltolan, yields derivatives **112** and **113**, respectively.²¹

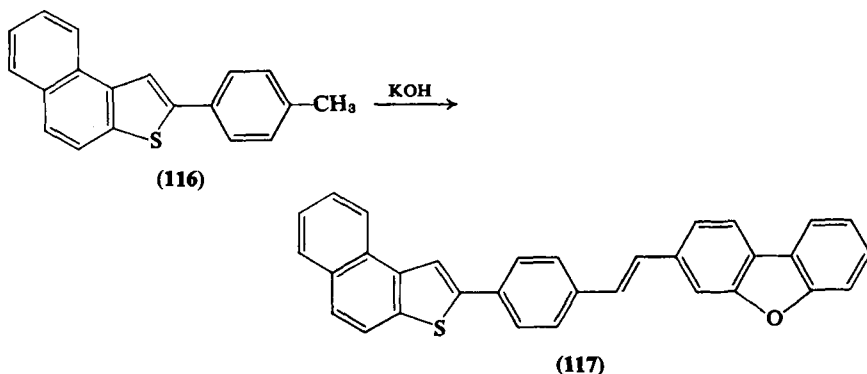


In the metallocene field, it has been observed that whereas 2-methylferrocene fails to react, methylcymantrene (**114**) indeed forms the thienyl derivative **115** on treatment with the anil from 2-formylthiophene and aniline.⁵⁵ It was also claimed that 5% of the *cis* isomer was isolated.

⁵⁵ R. Eberhardt and K. Schloegl, *Synth. React. Inorg. Met.-Org. Chem.* **4**, 317 (1974) [*CA* **82**, 57870 (1975)].

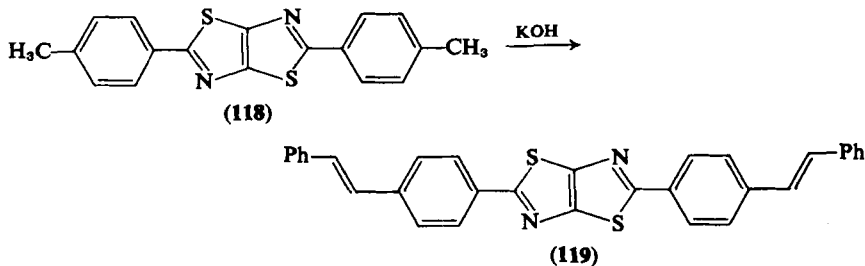


Finally, Schiff's bases of other heterocyclic aldehydes can also be reacted with *p*-tolyl-substituted benzo[*b*]- (see Table III) and naphtho[2,1-*b*]thiophenes.^{36,37,56} Thus, 2-(*p*-tolyl)naphtho[2,1-*b*]thiophene (116) gives, on reaction with the anil derived from 3-formyldibenzofuran and *p*-chloroaniline, the styryl compound 117.³⁸



B. THIAZOLES, BENZOTHAZOLES, AND 1,3,4-THIADIAZOLES

Both 2-(*p*-tolyl)-5-phenylthiazole and 2-(*p*-tolyl)benzothiazole can be converted to the corresponding stilbene derivatives (see Table IX) by reaction with aromatic aldehyde anils under the influence of potassium hydroxide.¹¹ Also, 2,5-bis(*p*-tolyl)thiazolo[5,4-*d*]thiazole (118) yields,



⁵⁶ G. Kormany, G. Kabas, H. Schlaepfer, and A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,535,614 (Swiss Appl. 1974).

with benzalaniline, the corresponding bis-stilbene (119).¹¹ Similarly, 2,5-di(*p*-tolyl)-1,3,4-thiadiazole (120) forms the 2,5-di(stilben-4-yl)-thiadiazole (121).¹¹

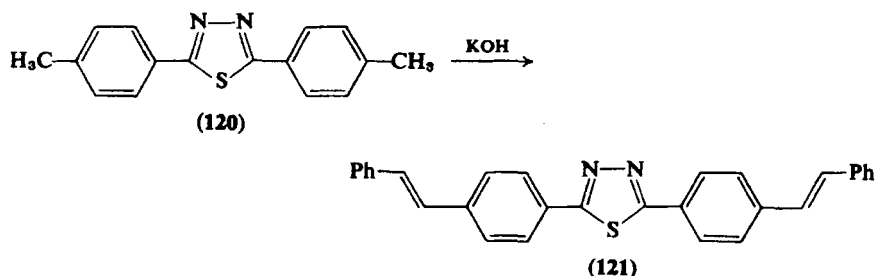
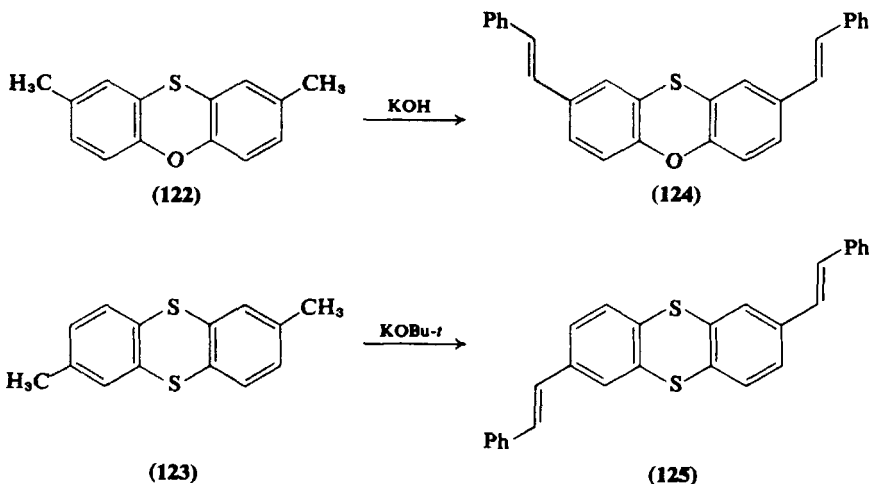


Table IX contains further stilbenyl derivatives of 2-(*p*-tolyl)-5-phenyl-1,3,4-thiadiazole. The reaction of Schiff's base from 3-formyldibenzofuran and *p*-chloroaniline with 2-(*p*-tolyl)-5-aryl-1,3,4-thiadiazoles has also been described.³⁶

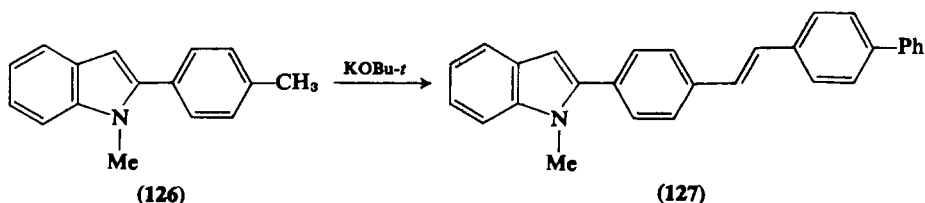
C. PHENOXATHIINS AND THIANTHRENES

From the field of six-membered sulfur-containing heterocycles, it has been shown that 2,8-dimethylphenoxathiin (122) and also 2,7-dimethylthianthrene (123) undergo reaction with anils, as exemplified by the formation of the respective distyryl derivatives 124 and 125 on treatment with benzalaniline.²⁶

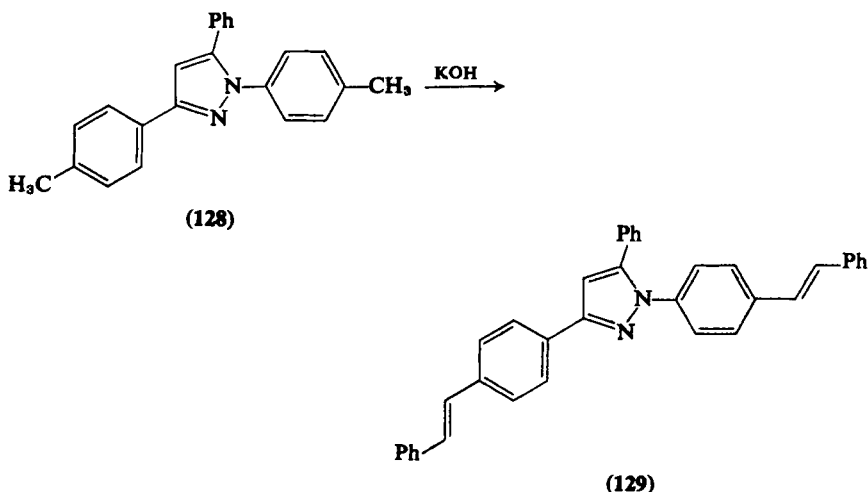


VIII. Indoles, Pyrazoles, Imidazoles, and Benzimidazoles

In the indole series, only one example has so far been reported, namely the formation of 1-methyl-2-(4-phenylstilben-4'-yl)indole (127) from 1-methyl-2-(*p*-tolyl)indole (126) and 4-phenylbenzaldehyde.²⁸

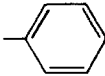
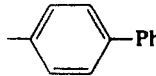
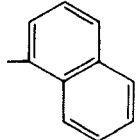
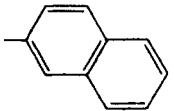
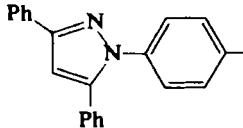
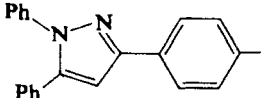


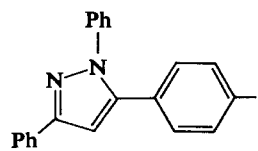
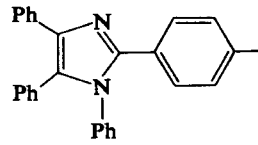
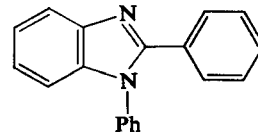
Pyrazoles substituted in the 1-, 3-, or 5-position with a *p*-tolyl group are converted to the corresponding stilbenyl derivatives, with benzalanilines in the presence of potassium hydroxide, only in very low yield (Table X). Thus, 1,3-di-(*p*-tolyl)-5-phenylpyrazole (128) reacts with benzalaniline to give only a 2% yield of the 1,3-di(stilben-4-yl)-5-phenylpyrazole (129).¹¹



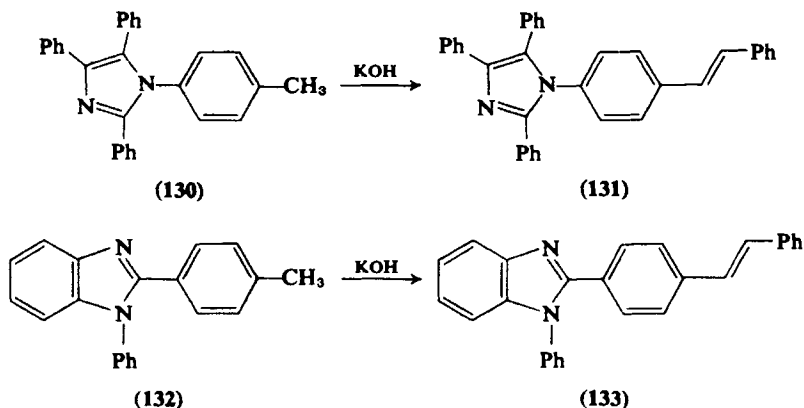
Improved yields are obtained from *p*-tolyl-substituted imidazoles and benzimidazoles provided that the 1-nitrogen atom is substituted. 1-(*p*-Tolyl)-2,4,5-triphenylimidazole (130) gives, with benzalaniline, 1-(stilben-4-yl)-2,4,5-triphenylimidazole (131), and 1-phenyl-2-(*p*-tolyl)-benzimidazole (132) the stilbenyl derivative 133.¹¹

TABLE X
STILBENYL DERIVATIVES OF PYRAZOLES, IMIDAZOLES, AND BENZIMIDAZOLES^a

M	A			
				
	6% 164°–165°C 329/392 nm	3% 212°–213°C 343/411 nm	— — —	— — —
	5% 216°–217°C 336/386 nm	1% 277°–278°C 351/411 nm	— — —	— — —

	5% 163°–164°C 327/388 nm	6% 208°–209°C 345/411 nm	— — —	— — —
	23% 253°–254°C 346/449 nm	45% 308°–309°C 359/463 nm	37% 230°–231°C 360/472 nm	34% 274°–275°C 357/462 nm
	33% 133°–134°C 338/404 nm	30% 196°–197°C 353/424 nm	30% 173°–174°C 353/433 nm	31% 207°–208°C 351/418 nm

^a From Siegrist and Meyer (Ref. 11).

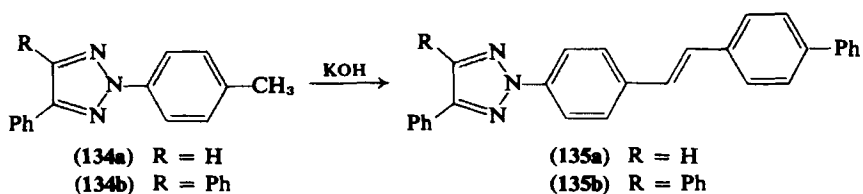


Further stilbenyl derivatives of imidazole and benzimidazole are shown in Table X.

IX. Triazoles and Condensed Triazoles

A. 2H-1,2,3-TRIAZOLES AND 1,2,4-TRIAZOLES

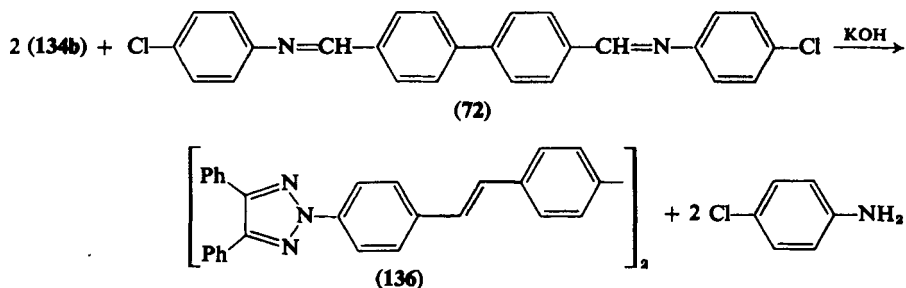
Reaction of *p*-tolyl substituted 2H-1,2,3-triazoles with anils of aromatic aldehydes was originally confined to the 2-(*p*-tolyl)-4-phenyl- and 2-(*p*-tolyl)-4,5-diphenyl-2H-1,2,3-triazoles (134a and b), which, with 4-phenylbenzaldehyde, gave the styryl derivatives 135a and b, respectively.⁵⁷



Furthermore, with Schiff's base 72 from 4,4'-diformylbiphenyl and *p*-chloroaniline, 134b yields the 4,4'-bis[4-(4,5-diphenyl-2H-1,2,3-triazol-2-yl)styryl]biphenyl (136).⁴³

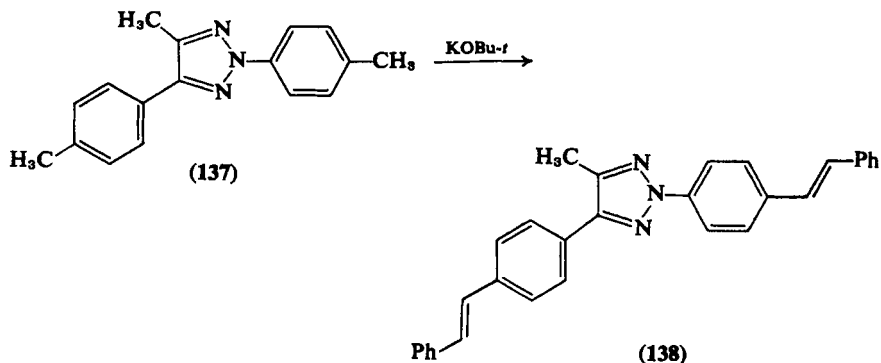
2,4-Di-(*p*-tolyl)-5-methyl-2H-1,2,3-triazole (137) was found to react with 2 moles of benzalaniline to give the distilbenyltriazole 138, where-

⁵⁷ A. E. Siegrist, P. Liechti, E. Maeder, and H. R. Meyer (Ciba-Geigy AG), Ger. Patent 1,594,834 (Swiss Appl. 1965 and 1966).

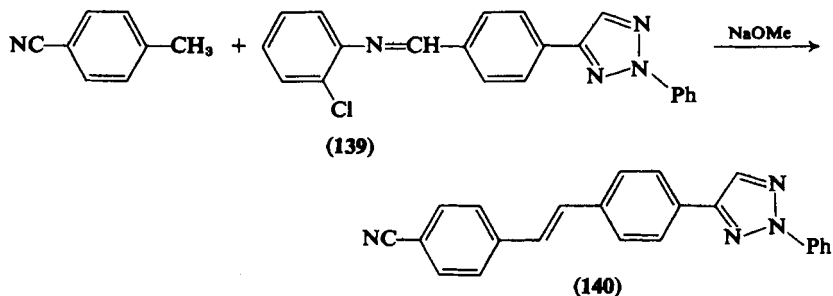


by the methyl group in the 5-position of the triazole ring did not react.⁵⁸

All remaining Anil Syntheses involving 1,2,3-triazoles have been performed with Schiff's bases derived from 4-formyl- or 2- or 4-(*p*-formylphenyl)-2*H*-1,2,3-triazole and chloroanilines, which react with both carbocyclic and heterocyclic *p*-tolyl derivatives. Carbocyclic

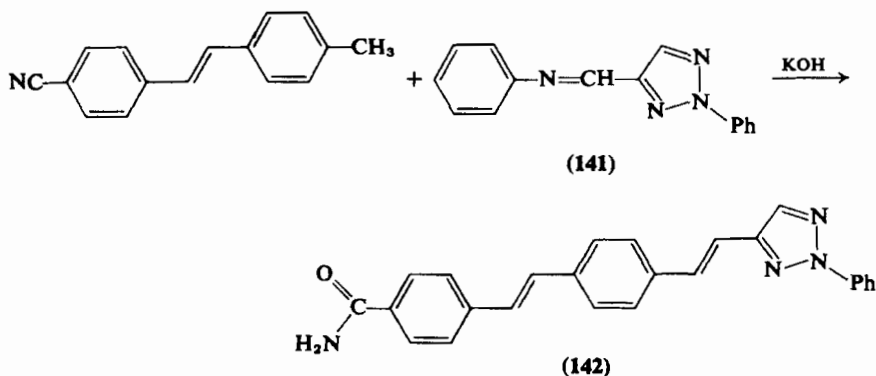


derivatives containing nitrile groups have been reacted, as exemplified by *p*-tolunitrile, which reacts with Schiff's base 139, in the presence of sodium methoxide, at room temperature, to give 2-phenyl-4-(4-cyano-stilben-4'-yl)-2*H*-1,2,3-triazole (140); the nitrile group is not affected.³⁹

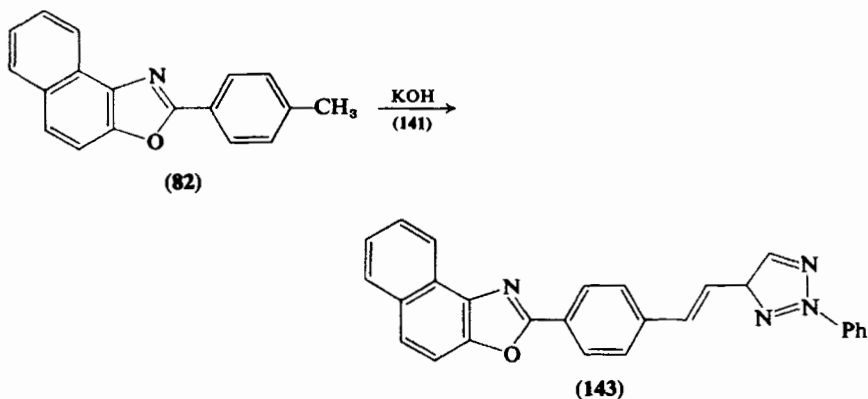


⁵⁸ K. Weber and R. Kirchmayr (Ciba-Geigy AG), Ger. Offen. 2,724,408 (Swiss Appl. 1976).

In the presence of potassium hydroxide, however, 4-cyano-4'-methylstilbene was found to react with Schiff's base **141** to give **142**, whereby during reaction the nitrile group was hydrolyzed to the amide.⁵⁹



The first example of the corresponding reaction with a *p*-tolyl-substituted heterocycle was that of 2-(*p*-tolyl)naphth[1,2-*d*]oxazole (**82**) which, with the anil **141**, gave the styryl compound **143**.⁶⁰

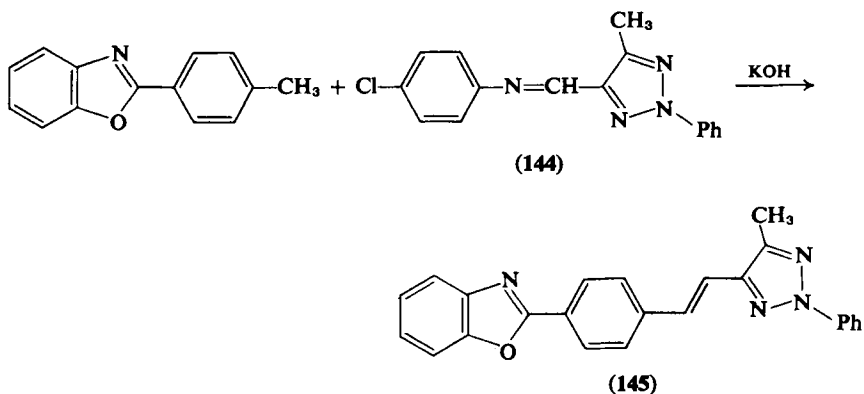


It was later discovered that the reaction of anils of 4-formyl- or 4-(*p*-formylphenyl)-2*H*-1,2,3-triazoles could be carried out with improved yields by working at room temperature and by irradiating the reaction mixture with ultraviolet light of wavelength > 300 nm during the initial 10 minutes of reaction. Thus 2-(*p*-tolyl)benzoxazole, when

⁵⁹ F. Fleck, H. Kittl, H.-R. Schmid, and S. Valenti (Sandoz AG), Ger. Offen. 2,212,480 (Swiss Appl. 1971).

⁶⁰ F. Fleck and H.-R. Schmid (Sandoz AG), U.S. Patent 3,891,632 (Swiss Appl. 1969).

reacted with Schiff's base **144**, gives the styryl compound **145** in 26% yield without, and in 59% yield with irradiation.^{61,62}



The previously mentioned ring-opening reaction of the 1,2,3-triazole ring (see Section II,E,1), which occurs concurrent to olefin formation, appears to be retarded on irradiation.⁶¹

Treatment of 2- or 4-(*p*-formylphenyl)-2*H*-1,2,3-triazoles with *p*-tolyl-substituted heterocycles such as benzo[*b*]furans,^{56,63} benzo[*b*]thiophenes,^{56,63} benzoxazoles,^{63,64} benzisoxazoles,⁵⁴ oxazoles,⁶³ isoxazoles,⁶³ oxadiazoles,^{63,65} benzotriazoles,⁶³ and *s*-triazolo[1,5-*a*]-pyridines¹⁹ has led to the formation of a number of new stilbene derivatives some of which are shown in Table XI.

Derivatives have also been obtained in which the 1,2,3-triazole ring is substituted by chlorine⁶³ and/or methoxy groups,⁶⁶ as, for example, in the formation of the stilbene **148** from 2-(*p*-tolyl)-5,7-dimethylbenzoxazole (**146**) and Schiff's base **147**.

In the 1,2,4-triazole field, the only examples of the Anil Synthesis to have been reported are the reactions of *p*-tolyl-substituted 1,2,4-triazoles with anils of aromatic aldehydes.¹¹ Thus, with 2 moles of benzalaniline,

⁶¹ A. E. Siegrist, G. Kormany, and G. Kabas, *Helv. Chim. Acta* **59**, 2469 (1976).

⁶² G. Kormany, G. Kabas, H. Schlaepfer, and A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,535,615 (Swiss Appl. 1974).

⁶³ A. E. Siegrist, G. Kormany, G. Kabas, and H. Schlaepfer, *Helv. Chim. Acta* **60**, 2334 (1977).

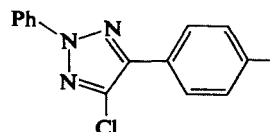
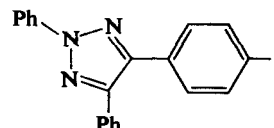
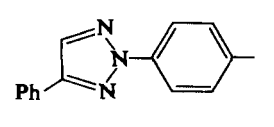
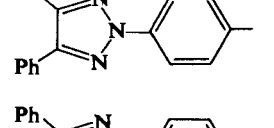
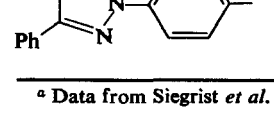
⁶⁴ G. Kormany, G. Kabas, H. Schlaepfer, and A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,535,613 (Swiss Appl. 1974).

⁶⁵ G. Kormany, G. Kabas, H. Schlaepfer, and A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,535,612 (Swiss Appl. 1974).

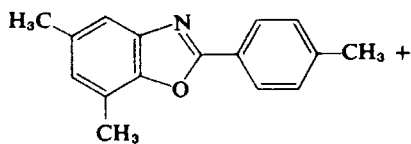
⁶⁶ H. Schlaepfer (Ciba-Geigy AG), Ger. Offen. 2,712,409 (Swiss Appl. 1976).

TABLE XI
STYRYL AND STILBENYL DERIVATIVES OF 2*H*-1,2,3-TRIAZOLES^a

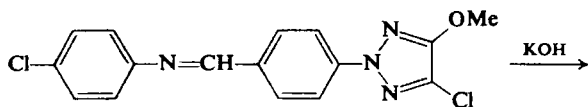
A	B			
	3% 195°–196°C 357/416 nm	66% 230°–231°C 351/410 nm	63% 256°–257°C 340/424 nm	68% 224°–225°C 343/407 nm
	— — —	42% 199°–200°C 362/426 nm	— — —	33% 228°–229°C 355/424 nm
	56% 274°–275°C 373/434 nm	75% 233°–234°C 367/429 nm	73% 201°–202°C 360/443 nm	74% 210°–211°C 362/426 nm

	— — —	38% 210°–211°C 366/426 nm	75% 192°–193°C 356/430 nm	61% 214°–215°C 358/421 nm
	49% 291°–292°C 369/435 nm	50% 244°–245°C 364/431 nm	81% 209°–210°C 355/445 nm	38% 219°–220°C 357/428 nm
	46% 288°–289°C 376/435 nm	72% 256°–257°C 369/434 nm	55% 228°–229°C 362/448 nm	75% 227°–228°C 363/432 nm
	— — —	47% 246°–247°C 369/430 nm	63% 207°–208°C 362/440 nm	38% 209°–210°C 363/425 nm
	31% 284°–284°C 377/438 nm	78% 253°–254°C 371/437 nm	66% 240°–241°C 365/452 nm	63% 246°–247°C 367/434 nm

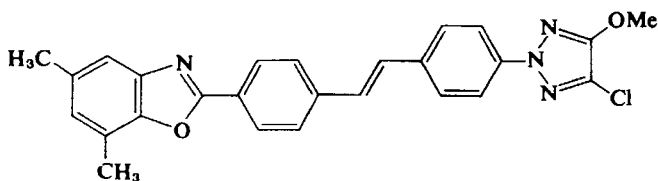
^a Data from Siegrist *et al.* for styryl (Ref. 61) and stilbenyl compounds (Ref. 63).



(146)

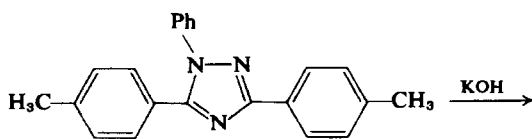


(147)

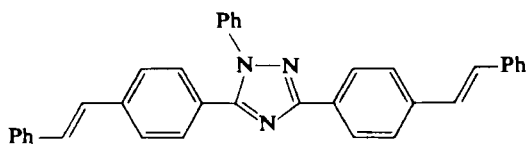


(148)

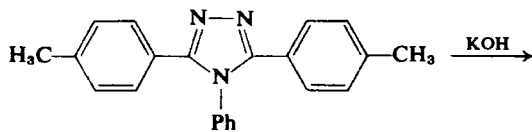
1-phenyl-3,5-di(*p*-tolyl)-1,2,4-triazole (149) yields the bis-stilbenyl compound 150, and 3,5-di(*p*-tolyl)-4-phenyl-1,2,4-triazole (151) yields the stilbene 68.



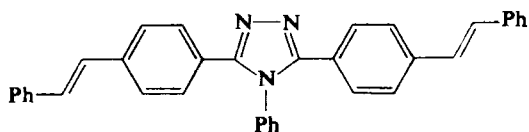
(149)



(150)



(151)

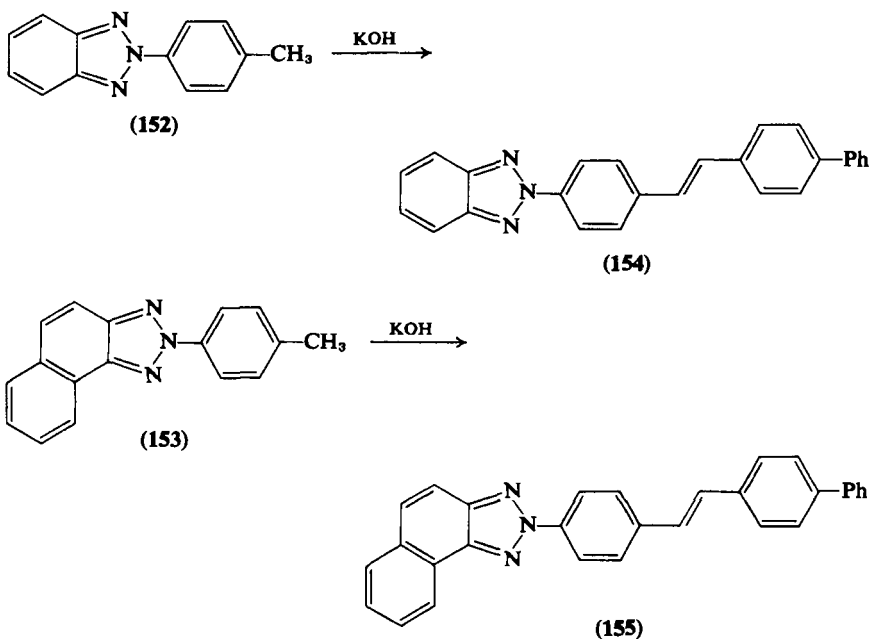


(68)

B. BENZOTRIAZOLES, NAPHTHO[1,2-*d*]TRIAZOLES, AND
BENZO[1,2-*d*:3,4-*d'*]BISTRIAZOLES

The benzotriazole ring system is remarkably stable toward alkali under the conditions of the Anil Synthesis, and hence relatively high reaction temperatures (up to 100°C) may be employed.

The first examples to be reported in this series were the reactions of 2-(*p*-tolyl)benzotriazole (**152**) and 2-(*p*-tolyl)naphtho[1,2-*d*]triazole (**153**) with 4-phenylbenzaldehyde, leading to the formation of the respective stilbene derivatives **154** and **155**.^{10,11} Later, the corresponding reaction of 2-(*p*-tolyl)-4,5,9',10'-phenanthrotriazole (**156**) yielding compound **157** was reported.⁶⁷

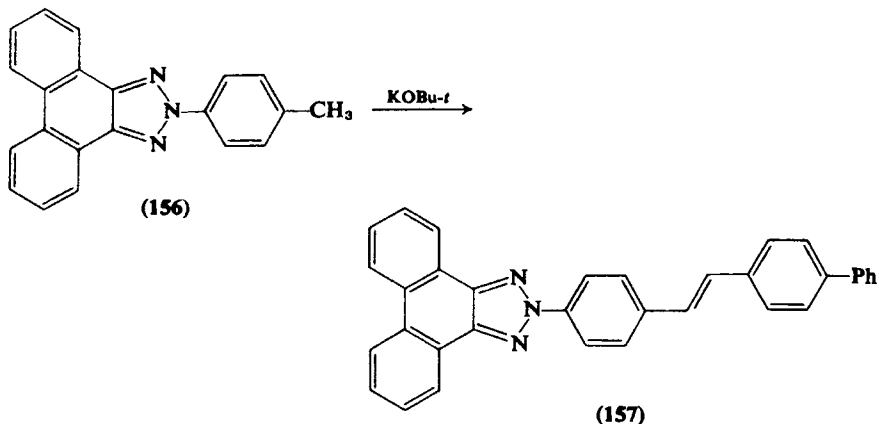


It was also established that Schiff's bases derived from *p*-chloroaniline are especially reactive toward 2-(*p*-tolyl)naphtho[1,2-*d*]triazole.⁶⁸

In the benzotriazole series, examples have been reported in which the benzo ring is substituted with methyl, alkoxy, phenoxy, and also chloro groups, whereby in particular the alkoxy groups exert a decisive effect on the position of the ultraviolet absorption and the fluorescence bands

⁶⁷ F. Fleck and H. Schmid (Sandoz AG), U.S. Patent 3,743,637 (Swiss Appl. 1970).

⁶⁸ M. Brunold and A. E. Siegrist, *Helv. Chim. Acta* **55**, 818 (1972).



(Table XII).⁶⁹ The stilbene part of such molecules may also be further substituted with alkyl, alkoxy, phenoxy, phenyl, chloro, or condensed benzo groups.⁶⁹ and, as was later reported, carboxylic acid groups and their esters⁷⁰ in addition to sulfonic acid groups.^{71,72}

It has further been observed⁶⁹ that methyl substituents in the benzo ring may undergo the Anil Synthesis. Thus, 2-(p-tolyl)-5-methylbenzotriazole (158) reacts with 2 moles of the anil derived from benzaldehyde and *p*-chloroaniline to yield 2-(stilben-4-yl)-5-styrylbenzotriazol (159).⁶⁹

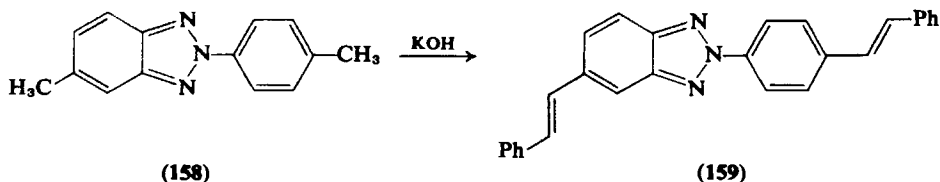


Table XII shows a further number of styryl and stilbenyl derivatives of benzo- and naphtho[1,2-*d*]triazole that have been obtained analogously.

A number of compounds in which two triazole rings are condensed on a single benzene nucleus have also been found to undergo the Anil Synthesis.⁷³⁻⁷⁵ For example, 2-(p-tolyl)-7-phenylbenzo[1,2-*d*:3,4-*d'*]bis-

⁶⁹ A. E. Siegrist and R. Zweidler, *Helv. Chim. Acta* **55**, 2300 (1972).

⁷⁰ H. R. Meyer and R. Zweidler (Ciba-Geigy AG), Ger. Offen. 2,539,461 and 2,539,537 (Swiss Appl. 1974).

⁷¹ H. R. Meyer (Ciba-Geigy AG), Ger. Offen. 2,525,682 (Swiss Appl. 1974).

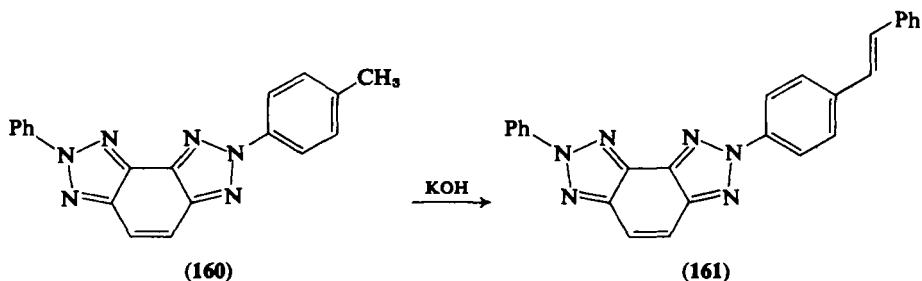
⁷² T. Noguchi and Y. Wakisaka (Nippon Kayaku Co., Ltd.), Jap. Patent Publ. 72-29,765 (Appl. 1969) [*CA* **78**, 17643 (1973)].

⁷³ A. E. Siegrist, *Helv. Chim. Acta* **55**, 2893 (1972).

⁷⁴ A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,804,773 (Swiss Appl. 1970).

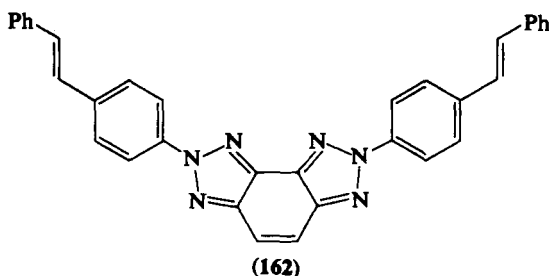
⁷⁵ A. E. Siegrist (Ciba-Geigy AG), Ger. Offen. 2,148,017 (Swiss Appl. 1970).

triazole (160) yields, with Schiff's base from benzaldehyde and *p*-chloroaniline, the stilbene derivative 161.^{73,74}



A series of stilbenyl derivatives with two condensed triazole rings is shown in Table XIII.

The distilbenyl derivative (162) has also been obtained similarly.^{73,75}



Of particular interest are cases in which substituents are present in ortho positions to the reacting methyl group. Apart from *o*-chloro-substituted derivatives, those with methoxy, carbonamido, sulfonamido, and phenylsulfonyl groups have been reported to undergo reaction.⁶⁸ The 2-(3-chloro-4-methylphenyl)-5-methoxybenzotriazole (163) has been found to be particularly reactive, yielding, with Schiff's base 98, the stilbene 164.⁵⁴

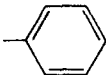
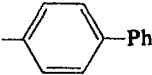
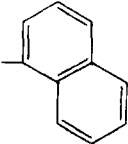
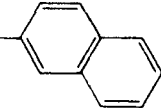
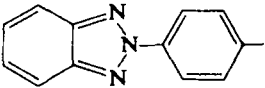
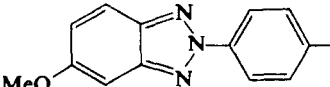
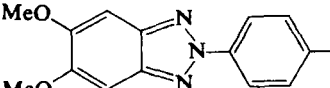
Further examples of the reaction products of *p*-tolyl-substituted benzo- and naphtho[1,2-*d*]triazoles with anils of heteroaromatic aldehydes are given in Table XIV.

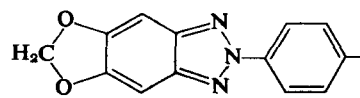
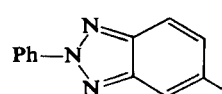
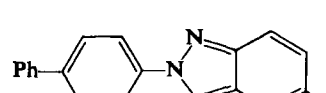
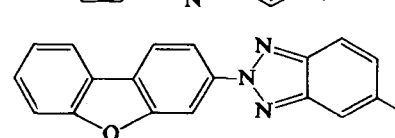
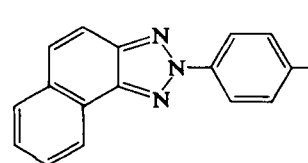
Finally, Schiff's bases derived from 2-(*p*-formylphenyl)-substituted triazoles and *p*-chloroaniline have also been found to form stilbenyl heterocycles.^{76,77} Thus, compound 163 gives, on reaction with Schiff's base 165, the bistriazolystilbene 166.

⁷⁶ A. E. Siegrist, *Helv. Chim. Acta* 57, 81 (1974).

⁷⁷ A. E. Siegrist (Ciba-Geigy AG), U.S. Patent 3,793,315 (Swiss Appl. 1970).

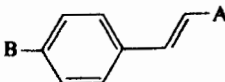
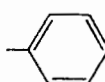
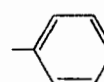
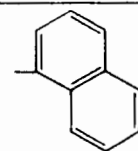
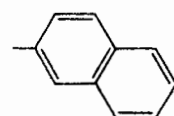
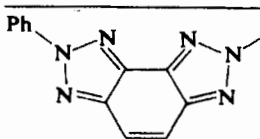
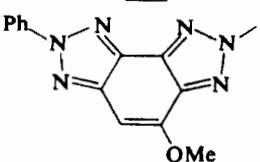
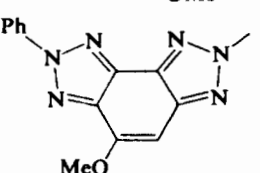
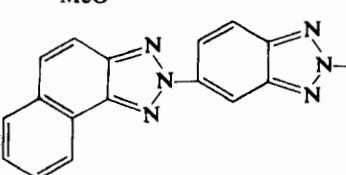
TABLE XII
STYRYL DERIVATIVES OF CONDENSED TRIAZOLES^a

M	A			
				
	85% 197°–198°C 352/446 nm	84% 270°–271°C 364/463 nm	59% 168°–169°C 359/476 nm	82% 221°–222°C 359/460 nm
	71% 177°–178°C 358/432 nm	76% 262°–263°C 365/448 nm	— — —	— — —
	64% 222°–223°C 362/416 nm	66% 281°–282°C 372/431 nm	87% 245°–246°C 370/441 nm	34% 273°–274°C 369/430 nm

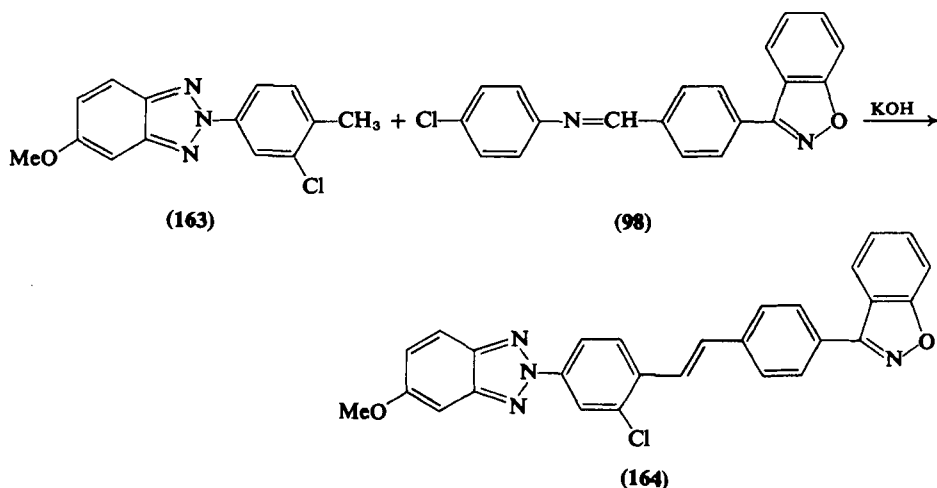
	65% 254°–255°C 361/420 nm	65% 297°–298°C 369/433 nm	72% 235°–236°C 370/445 nm	64% 281°–282°C 370/433 nm
	38% 156°–157°C 354/437 nm	74% 203°–204°C 363/453 nm	— — —	— — —
	78% 202°–203°C 363/443 nm	73% 288°–289°C 373/455 nm	60% 182°–183°C 370/474 nm	79% 245°–246°C 373/455 nm
	83% 236°–237°C 371/441 nm	66% 263°–264°C 378/463 nm	60% 195°–196°C 374/482 nm	70% 256°–257°C 376/462 nm
	39% 182°–183°C 366/432 nm	86% 255°–256°C 373/446 nm	59% 215°–216°C 373/461 nm	64% 236°–237°C 373/448 nm

* From Siegrist and co-workers (Refs. 11, 36, 68, and 69).

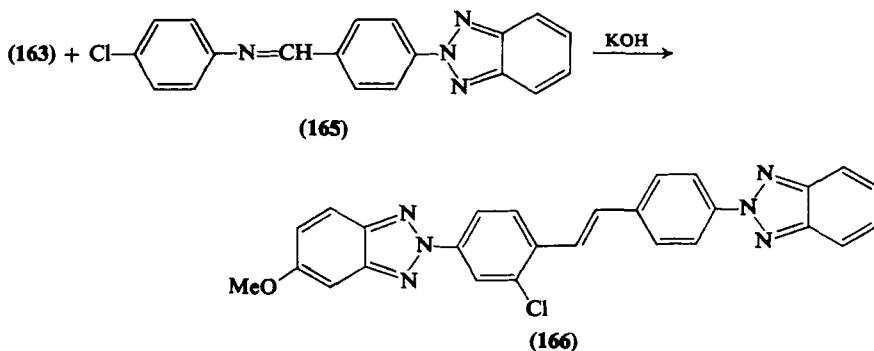
TABLE XIII: STILBENYL DERIVATIVES OF CONDENSED TRIAZOLOTRIAZOLES^a

B	A			
				
				
	83% 254°–255°C 351/440 nm	79% 314°–315°C 365/454 nm	71% 233°–234°C 361/466 nm	43% 290°–291°C 360/452 nm
	55% 211°–212°C 346/434 nm	70% 297°–298°C 364/449 nm	— — —	61% 237°–238°C 356/448 nm
	59% 254°–255°C 358/421 nm	75% 317°–318°C 371/435 nm	67% 209°–210°C 366/445 nm	71% 296°–297°C 367/432 nm
	78% 259°–260°C 378/475 nm	74% 304°–305°C 383/500 nm	— — —	— — —

^a From Siegrist and Zweidler (Ref. 69) and Siegrist (Ref. 73).



Further reaction products of Schiff's bases of 2-(*p*-formylphenyl)-substituted condensed triazoles with *p*-tolyl heterocycles are listed in Table XV.



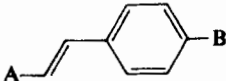
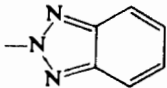
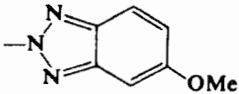
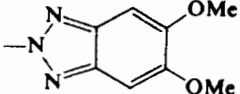
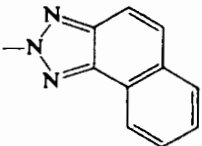
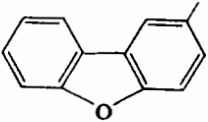
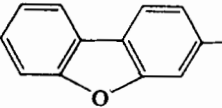
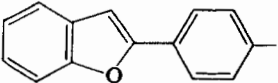
X. Imidazo[1,2-*a*]- and *s*-Triazolo[1,5-*a*]pyridines

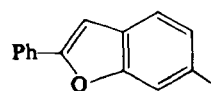
Of the condensed heterocycles containing a bridgehead nitrogen atom that have been subjected to the Anil Synthesis, the 2-arylimidazo[1,2-*a*]-pyridine system exhibits good alkali stability, whereas the 2-aryl-*s*-triazolo[1,5-*a*]pyridine system may only be reacted below 45°C.^{19,78}

2-(*p*-Tolyl)imidazo[1,2-*a*]pyridine (167) reacts with Schiff's base from 4-formylbiphenyl and *p*-chloroaniline to give only a 9% yield of the

⁷⁸ J.-P. Pauchard and A. E. Siegrist, *Helv. Chim. Acta* **61**, 129 (1978).

TABLE XIV
HETEROCYCLIC STYRYL DERIVATIVES OF CONDENSED TRIAZOLES^a

				
A	B			
				
	36% 214°–215°C 356/468 nm	79% 202°–203°C 366/451 nm	15% 294°–295°C 370/432 nm	48% 266°–267°C 367/452 nm
	73% 273°–274°C 368/466 nm	40% 226°–227°C 370/446 nm	18% 261°–262°C 376/434 nm	64% 243°–244°C 377/447 nm
	34% 335°–336°C 383/482 nm	16% 335°–336°C 385/463 nm	4% 333°–334°C 386/447 nm	28% 296°–297°C 387/462 nm

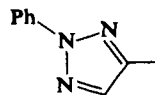


82%
246°–247°C
379/507 nm

77%
239°–240°C
383/486 nm

6%
230°–231°C
385/454 nm

80%
242°–243°C
385/483 nm

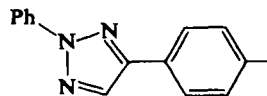


10%
235°–236°C
353/436 nm

—
—
—

—
—
—

70%
272°–273°C
369/426 nm

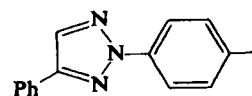


40%
235°–236°C
368/454 nm

43%
247°–248°C
372/442 nm

22%
277°–278°C
375/433 nm

—
—
—

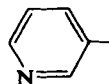


57%
257°–258°C
370/457 nm

50%
240°–241°C
373/443 nm

15%
238°–239°C
378/434 nm

—
—
—



36%
199°–200°C
349/429 nm

36%
188°–189°C
359/415 nm

16%
205°–206°C
363/413 nm

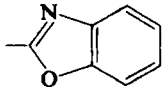
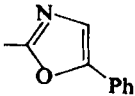
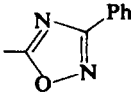
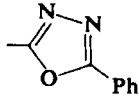
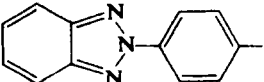
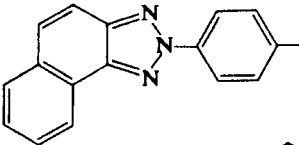
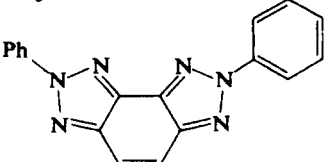
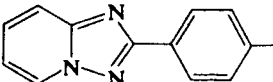
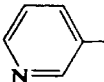
41%
194°–195°C
365/419 nm

^a From Siegrist and co-workers (Refs. 33, 36, 37, 61, 63).

Sec. X]

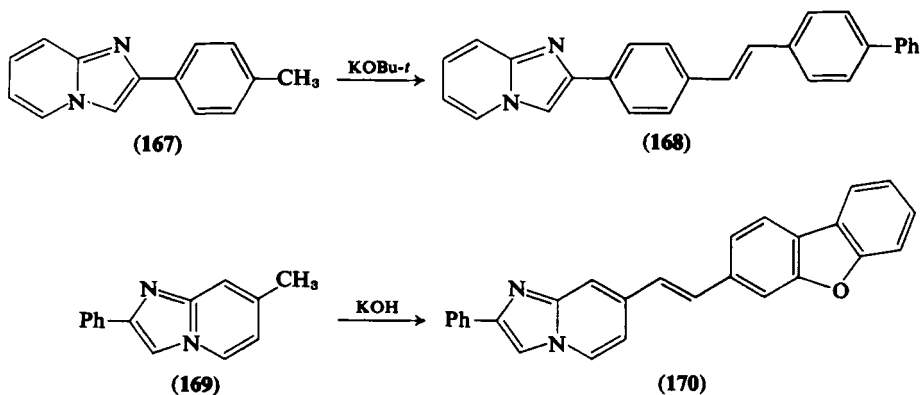
OLEFIN SYNTHESIS WITH ANILIS

TABLE XV
OXAZOLYL AND OXADIAZOLYL STYRENES^a

A	B			
				
	32% > 360°C 374/437 nm	— — —	41% 266°–267°C 368/430 nm	— — —
	52% 306°–307°C 382/442 nm	14% 260°–261°C 386/449 nm	67% 255°–256°C 378/439 nm	51% 262–263°C 379/437 nm
	55% 364°–355°C 377/437 nm	— — —	— — —	46% 341°–342°C 373/433 nm
	65% > 360°C 363/422 nm	38% 259°–260°C 372/436 nm	74% 287°–288°C 355/424 nm	65% 280°–281°C 357/415 nm
	12% 190°–191°C 348/399 nm	50% 162°–163°C 356/438 nm	39% 174°–175°C 335/394 nm	25% 168°–169°C 342/390 nm

^a From Siegrist and co-workers (Refs. 19, 33, and 76).

stilbene (**168**). 2-Phenyl-7-methylimidazo[1,2-*a*]pyridine (**169**), however, is far more reactive, giving, with the anil from 3-formyldibenzofuran and *p*-chloroaniline, the ethylene derivative **170** in 70% yield and under relatively mild conditions.⁷⁸



Further styryl derivatives of 2-phenylimidazo[1,2-*a*] and of 2-phenyl-*s*-triazolo[1,5-*a*]pyridine are listed in Table XVI.

As previously mentioned, the methyl group of 2-(*p*-tolyl)-*s*-triazolo[1,5-*a*]pyridine is inert under the conditions of the Anil Synthesis. However, introduction of a chlorine atom in ortho position to this methyl group enables reaction to be carried out at 20°–30°C (Section II,E,3). Thus, for example, from 2-(3-chloro-4-methylphenyl)-*s*-triazolo[1,5-*a*]pyridine (**19**) and Schiff's base **171**, the stilbene **172** is formed. In the case of 2-phenyl-7-methyl-*s*-triazolo[1,5-*a*]pyridine (**173**), however, reaction with **171** gives the styryl derivative **174**, without additional activation of the methyl group.¹⁹

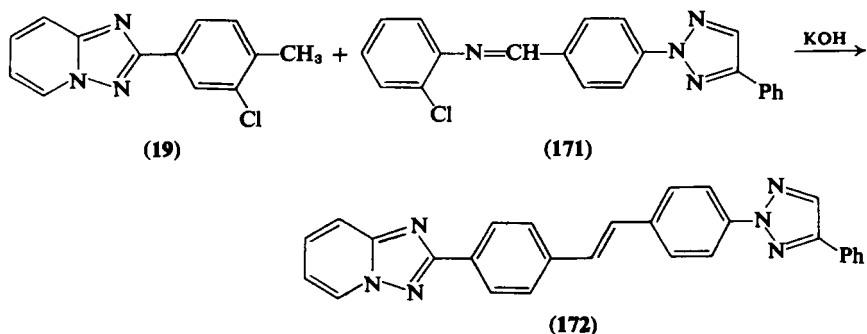
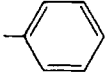
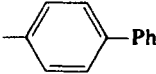
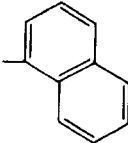
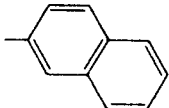
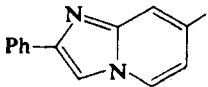
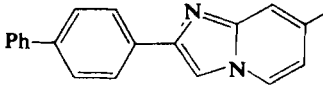
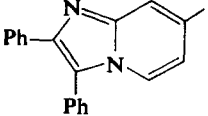
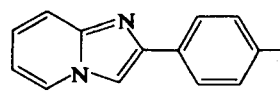
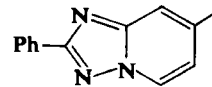
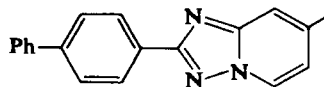
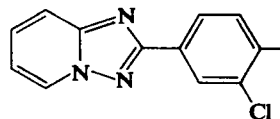
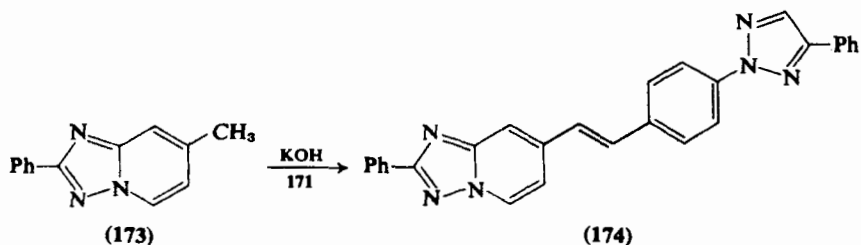


TABLE XVI
STYRYL DERIVATIVES OF IMIDAZO[1,2-*a*]- AND *s*-TRIAZOLO[1,5-*a*]PYRIDINES^a

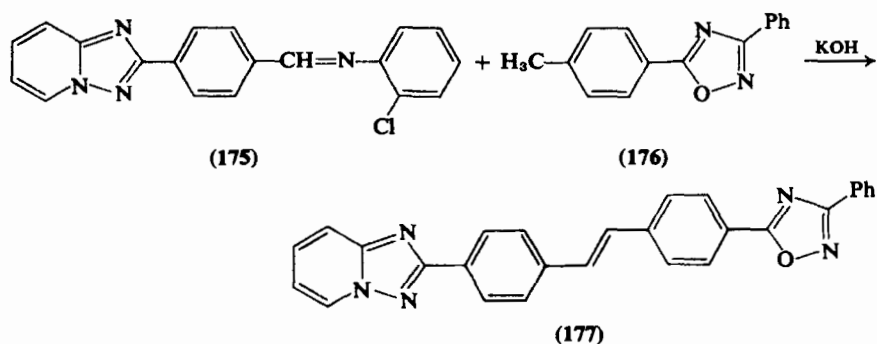
M	A			
	   			
	58% 207°–208°C 359/423 nm	67% 274°–275°C 370/443 nm	45% 189°–190°C 375/452 nm	66% 264°–265°C 369/438 nm
	76% 276°–277°C 365/428 nm	75% 347°–348°C 375/445 nm	66% 220°–221°C 378/454 nm	68% 319°–320°C 373/443 nm
	48% 142°–143°C 365/446 nm	76% 246°–247°C 376/463 nm	— — —	— — —

	8% 261°–262°C 349/412 nm	9% 323°–324°C 361/422 nm	— — —	— — —
	32% 170°–171°C 327 nm/—	57% 222°–223°C 344/404 nm	53% 178°–179°C 350/425 nm	55% 207°–208°C 338/405 nm
	49% 243°–244°C 329 nm/—	77% 283°–284°C 345/404 nm	49% 194°–195°C 349/422 nm	71% 271°–272°C 340/402 nm
	42% 207°–208°C 355 nm/—	76% 265°–266°C 350/422 nm	68% 210°–211°C 348/435 nm	66% 244°–245°C 345/414 nm

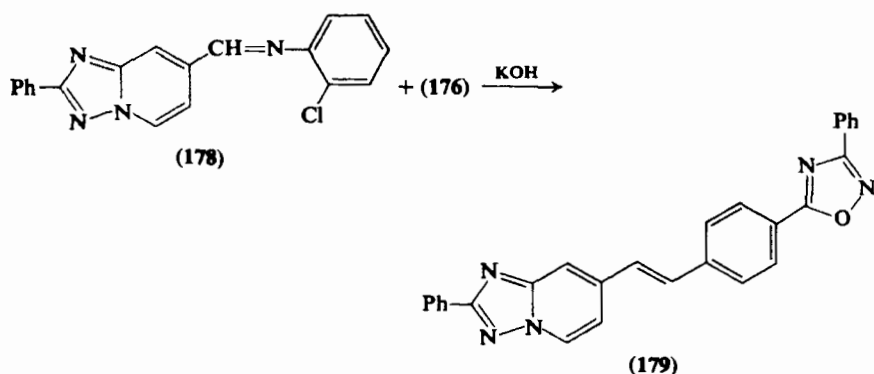
^a Data from Pauchard and Siegrist for imidazopyridines (Ref. 78) and for triazolopyridines. (Ref. 19).



Of the various Schiff's bases derived from formyl-2-phenyl-*s*-triazolo[1,5-*a*]pyridines and *o*-chloroaniline, the most reactive is that of 2-(*p*-formylphenyl)-*s*-triazolo[1,5-*a*]pyridine (175), which gives, readily and in good yield (74%), with 3-phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole (176), the stilbene 177.¹⁹



In comparison, however, isomeric Schiff's base from 2-phenyl-7-formyl-*s*-triazolo[1,5-*a*]pyridine (178) is far less reactive and gives, with 176, the styryl derivative 179 in a yield of only 9%.¹⁹

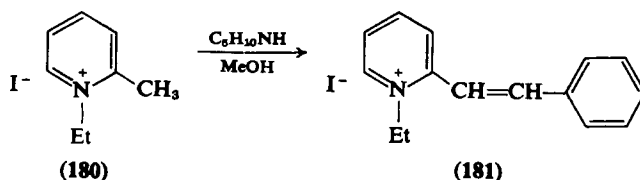


Further styryl derivatives obtained from Schiff's bases **175** and **178** are shown in Tables XV and XVII.

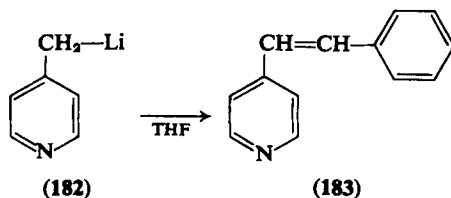
XI. Nitrogen-Containing Six-Membered Rings

A. PYRIDINES, PYRIMIDINES, 1,2,4- AND 1,3,5-TRIAZINES

The formation of styryl pyridines by condensation of anils with picolines was first reported by Crippa and Maffei.^{79,80} These workers found that 2-picoline ethiodide (**180**) reacted with benzalaniline in methanol in the presence of piperidine to give 2-styrylpyridine ethiodide (**181**). However, it was also reported that 3-picoline ethiodide and 2-picoline itself failed to react under these conditions.



It has also been reported that 4-picollyllithium (**182**) adds to benzalaniline and leads, with elimination of aniline, to 4-stilbazole (**183**).⁸¹



Such reactions are, however, not unexpected, as the reactivity of the methyl groups in 2- and 4-picolines is well documented, as exemplified by their condensation with aromatic aldehydes to give trans 2- and 4-styrylpyridines.⁸²

Recently, however, it has been reported that treatment of 2,6-dimethylpyridine (**184**) with benzalaniline leads to a 78% yield of 2,6-distyrylpyridine (**185**), as opposed to less than 45% with the corresponding aldehyde.⁸³

⁷⁹ G. B. Crippa and S. Maffei, *Rend. Ist. Lombardo Sci.* **76**, 217 (1943) [*CA* **43**, 2209 (1949)].

⁸⁰ G. B. Crippa and S. Maffei, *Gazz. Chim. Ital.* **77**, 416 (1947) [*CA* **42**, 2373 (1948)].

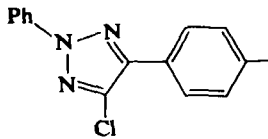
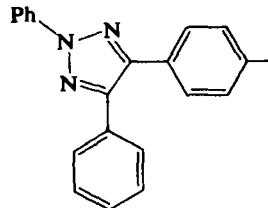
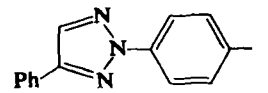
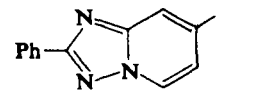
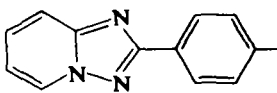
⁸¹ M. E. Derieg, I. Douvan, and R. I. Fryer, *J. Org. Chem.* **33**, 1290 (1968).

⁸² G. Galiazzo, *Gazz. Chim. Ital.* **95**, 1322 (1965) [*CA* **64**, 17532 (1966)].

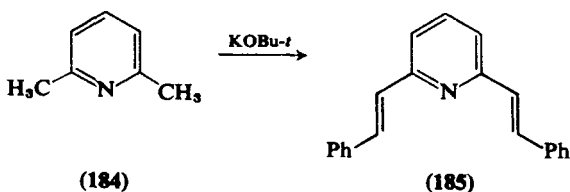
⁸³ G. R. Newkome and J. M. Robinson, *Tetrahedron Lett.*, 691 (1974).

TABLE XVII
CHLORINE-CONTAINING STYRYL DERIVATIVES^a

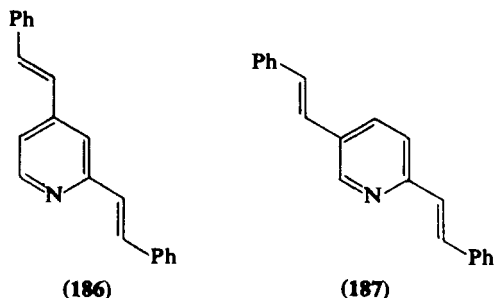
		B			
A					
		61% 241°–242°C 371/453 nm	81% 242°–243°C 355/444 nm	— — —	82% 267°–268°C 359/425 nm
		47% 231°–232°C 360/425 nm	69% 268°–269°C 340/409 nm	68% 281°–282°C 352/418 nm	58% 254°–255°C 348/408 nm
		63% 234°–235°C 369/448 nm	82% 211°–212°C 353/434 nm	44% 254°–255°C 363/445 nm	78% 264°–265°C 356/422 nm

	60% 227°–228°C 365/438 nm	70% 220°–221°C 348/424 nm	52% 253°–254°C 360/440 nm	49% 236°–237°C 350/418 nm
	43% 129°–130°C 364/446 nm	71% 208°–209°C 347/439 nm	59% 279°–280°C 356/449 nm	47% 226°–227°C 348/424 nm
	56% 232°–233°C 367/457 nm	82% 247°–248°C 354/442 nm	45% 249°–250°C 364/451 nm	76% 291°–292°C 358/424 nm
	46% 277°–278°C 363/421 nm	— — —	27% 301°–302°C 357/417 nm	— — —
	83% 330°–331°C 367/432 nm	— — —	86% 322°–323°C 361/427 nm	— — —

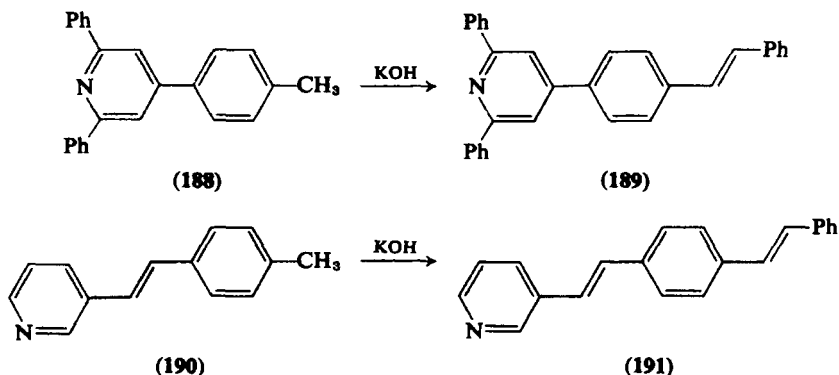
^a From Siegrist and co-workers (Refs. 19, 36, 37, 54).



It has also been found that both 2,4- and, of particular interest, 2,5-dimethylpyridines react with Schiff's base from benzaldehyde and *p*-chloroaniline, in the presence of potassium hydroxide, to give the respective distyrylpyridines **186** and **187** (Table XVIII).³⁴

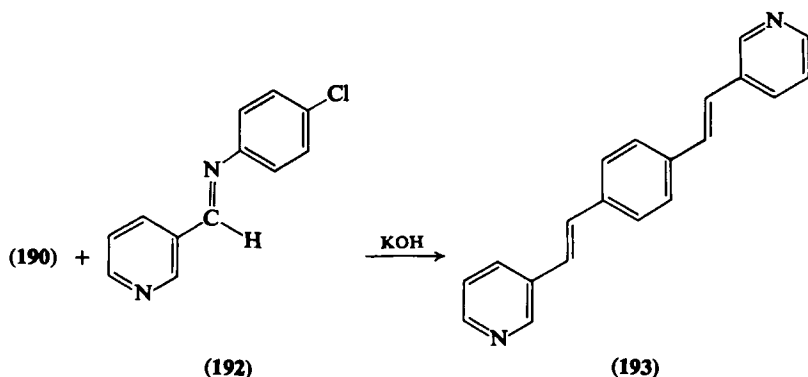


Apart from methyl-substituted pyridines, *p*-tolyl- and 4-methylstyrylpyridines have also been found to react with benzalaniline. Thus, 2,6-diphenyl-4-(*p*-tolyl)pyridine (**188**) gives the stilbenyl derivative **189**, and the stilbazole **190** gives 4-[β -(3-pyridyl)vinyl]stilbene (**191**) (Table XIX).³⁴



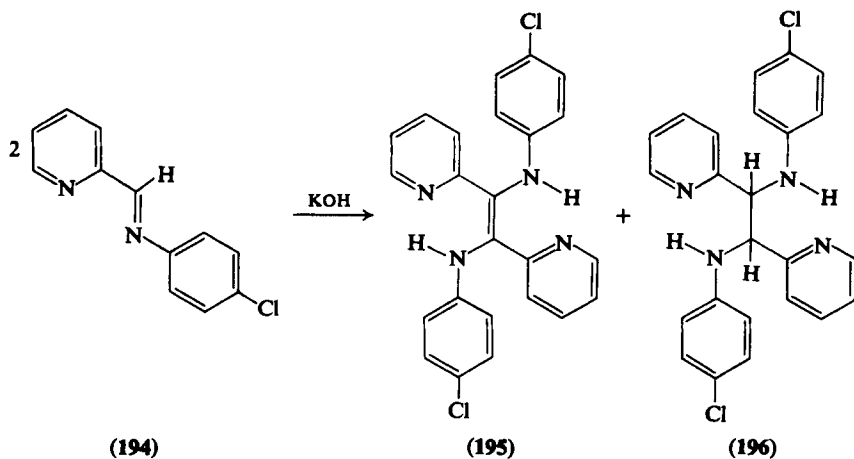
Tables XVIII and XX contain a number of di- and tristyrylpyridine derivatives.

Of the pyridine aldehydes, only Schiff's bases (192) from 3-formylpyridine and anilines such as *p*-chloroaniline, which with the stilbazole 190 forms 1,4-bis[β -(3-pyridyl)vinyl]benzene (193), have been found to undergo the Anil Synthesis.³⁴



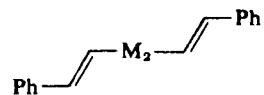
Further reaction products of the anil 192 with *p*-tolyl-substituted heterocycles are shown in Tables XIV and XV, and structures 46, 69, and 83.

Schiff's base from 2-formylpyridine and *p*-chloroaniline (194) yields in the presence of potassium hydroxide at room temperature, among other products, 1,2-di(*p*-chloroanilino)-1,2-di(2-pyridyl)ethene (195) and the corresponding alkane (196).³⁴ This dimerization reaction has been

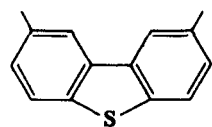


previously reported by Newkome and Robinson in the case of the anil from 2-formylpyridine and aniline.⁸³

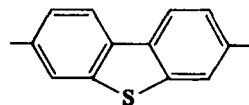
TABLE XVIII: DISTYRYL DERIVATIVES



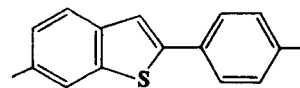
M_2		Ref.	M_2		Ref.
	27% 201°–202°C 362/426 nm	20		68% 292°–293°C 360/413 nm	21
	54% 330°–331°C 354/421 nm	21		59% 356°–357°C 385/453 nm	21
	48% 185°–186°C 375/463 nm	21		82% 317°–318°C 362/422 nm	21
	48% 190°–191°C 355/436 nm	21		76% 293°–294°C 369/423 nm	26
	36% 149°–150°C 323/416 nm	21		42% 272°–273°C 382/453 nm	26
				50% 335°–336°C 396/465 nm	26



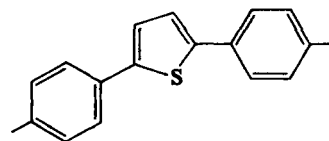
5%
209°-210°C
319/388 nm



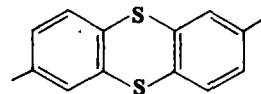
80%
311°-312°C
366/420 nm



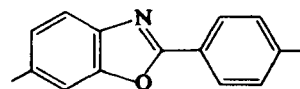
41%
338°-339°C
383/447 nm



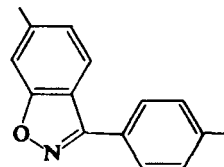
68%
346°-347°C
397/470 nm



57%
258°-259°C
329 nm/—

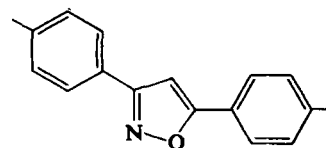


2%
260°-261°C
372/472 nm



74%
248°-249°C
336/410 nm

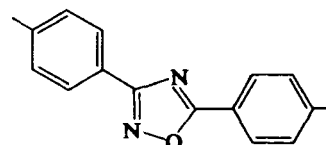
26



46%
311°-314°C
342/390 nm

11

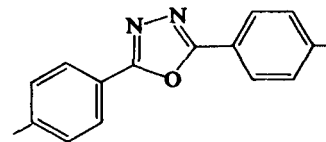
26



21%
246°-247°C
337/408 nm

11

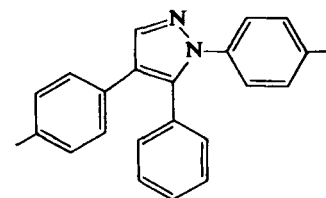
26



57%
279°-280°C
360/418 nm

11

26

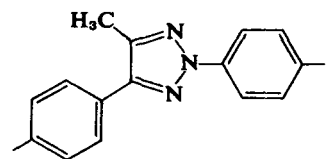


2%
236°-237°C
340/405 nm

11

26

11



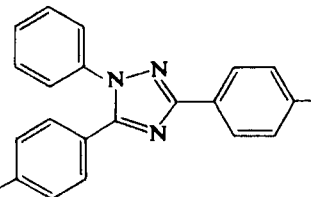
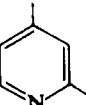
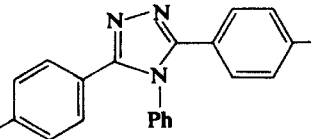
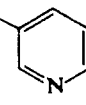
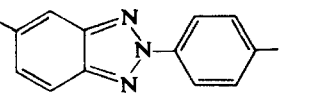
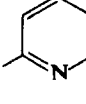
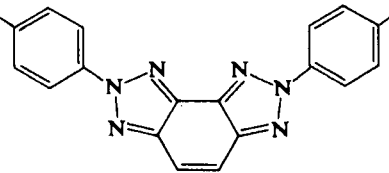
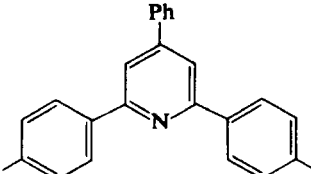
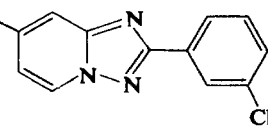
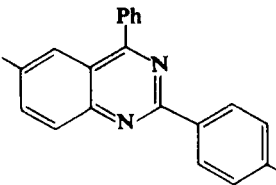
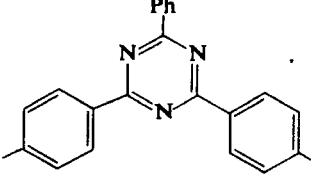
72%
216°-217°C
355/415 nm

58

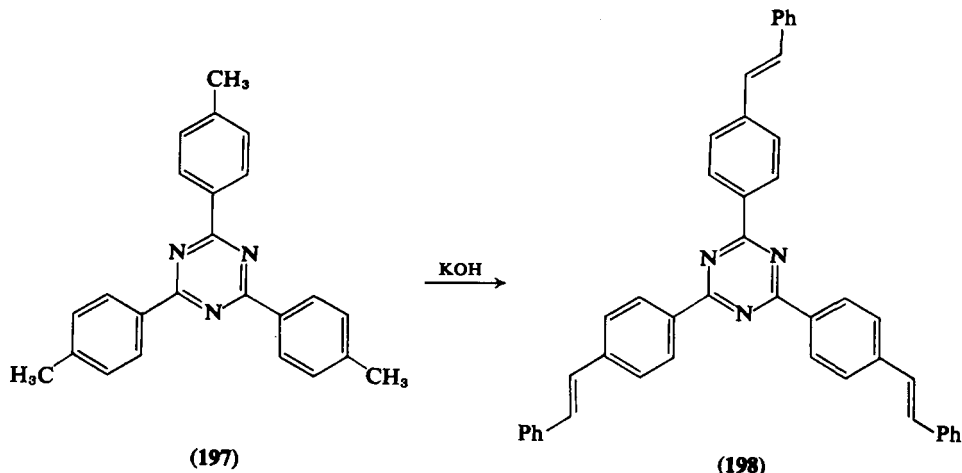
54

(continued)

TABLE XVIII—continued

M_2	Ref.	M_2	Ref.
	11		34
22% 219°–220°C 336/392 nm		10% 172°–173°C 311/417 nm	
	11		34
56% 343°–344°C 338/413 nm		30% 208°–209°C 361/427 nm	
	69		34
85% 224°–225°C 379/445 nm		53% 166°–167°C 293/387 nm	
	73		11
85% > 360°C 360/436 nm		9% 256°–257°C 331/391 nm	
	19		11
65% 219°–220°C 335/398 nm		55% 290°–291°C 363/466 nm	
			11
		26% 241°–242°C 356/455 nm	

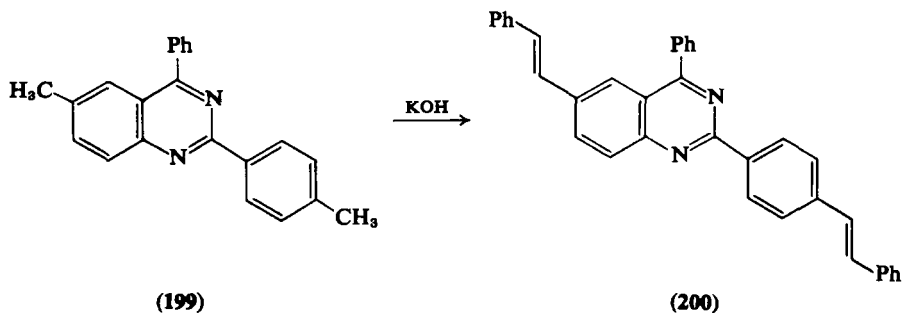
Finally, *p*-tolyl-substituted pyrimidines and 1,2,4- and 1,3,5-triazines have been found also to undergo the Anil Synthesis,¹¹ whereby several products have been patented as fluorescent whitening agents.⁸⁴ Thus, for example, 2,4,6-tri(*p*-tolyl)-1,3,5-triazine (197) reacts with 3 moles of benzalaniline to yield the tristilbenyl derivative 198.



Further di- and tristilbenyl derivatives of pyrimidines and 1,3,5-triazines are shown in Tables XVIII and XX.

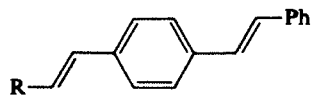
B. QUINAZOLINES AND QUINOXALINES

In the case of quinazolines and quinoxalines, both *p*-tolyl groups and also methyl groups attached to the condensed benzene ring have been found to react with benzalaniline.¹¹ For example, 2-(*p*-tolyl)-4-phenyl-6-methylquinazoline (199) gives, with benzalaniline, 2-(stilben-4-yl)-4-

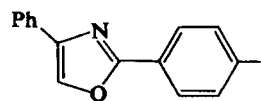


⁸⁴ A. E. Siegrist, P. Liechti, E. Maeder, L. Guglielmetti, and H. R. Meyer (Ciba-Geigy AG), U.S. Patents 3,758,462 and 3,849,163 (Swiss Appl. 1965 and 1966).

TABLE XIX
STYRYL STILBENE DERIVATIVES

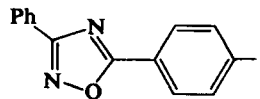


R		Ref.	R		Ref.
	16% 261°–262°C 359/423 nm	36		41% > 355°C 384/449 nm	37
	68% 293°–294°C 373/433 nm	36		80% 323°–324°C 383/469 nm	37
	40% > 355°C 386/448 nm	37		55% 269°–270°C 367/448 nm	54
	33% 290°–291°C 382/449 nm	37			
	7% 258°–259°C 368/431 nm	21		65% 201°–202°C 366/451 nm	54



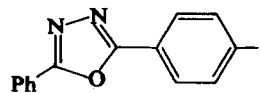
12%
255°–256°C
385/452 nm

37



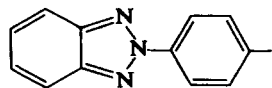
73%
217°–218°C
376/483 nm

37



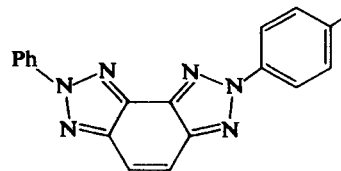
57%
253°–254°C
376/464 nm

37



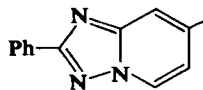
49%
315°–316°C
382/486 nm

37



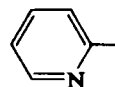
65%
327°–328°C
382/475 nm

37



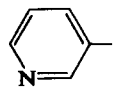
74%
227°–228°C
369/444 nm

19



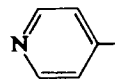
44%
220°–221°C
359/423 nm

34



62%
232°–233°C
357/417 nm

34



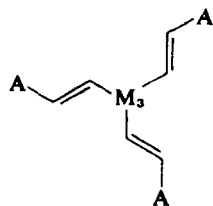
40%
283°–284°C
358/447 nm

34

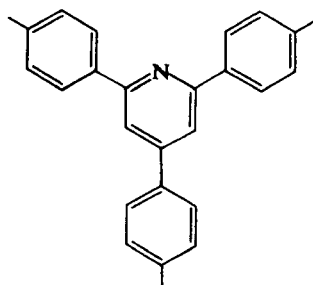
Sec. XI.B]

OLEFIN SYNTHESIS WITH ANILS

TABLE XX
TRISTILBENYL DERIVATIVES^a



M_3	A			
	46% 212°–213°C 337/388 nm	9% 349°–350°C 353/411 nm	41% 276°–277°C 353/421 nm	5% 269°–270°C 349/408 nm

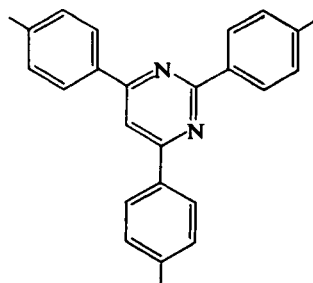


41%
194°–195°C
342/415 nm

56%
347°–350°C
360/424 nm

—
—
—

—
—
—

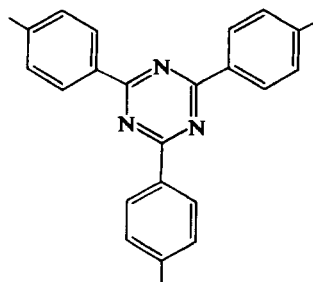


33%
247°–248°C
349/439 nm

32%
345°–347°C
367/457 nm

35%
288°–289°C
370/476 nm

57%
281°–282°C
373/458 nm



15%
294°–295°C
360/460 nm

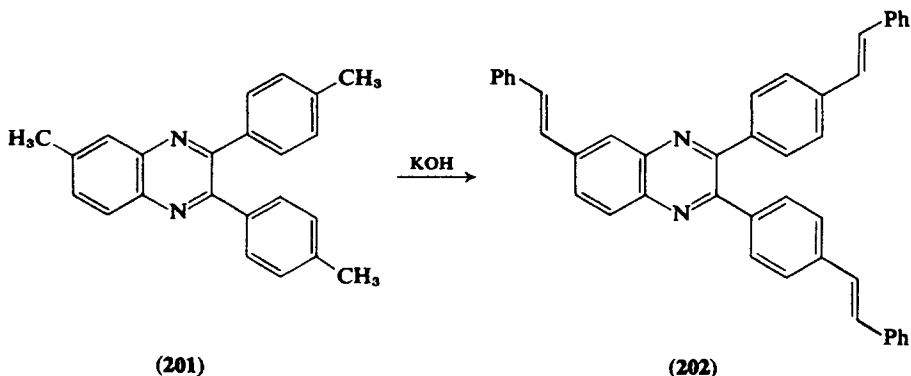
36%
361°–362°C
375/484 nm

—
—
—

—
—
—

^a From Siegrist and co-workers (Refs. 11 and 21).

phenyl-6-styrylquinazoline (**200**), and 2,3-di(*p*-tolyl)-6-methylquinoxaline (**201**) gives product **202**.¹¹

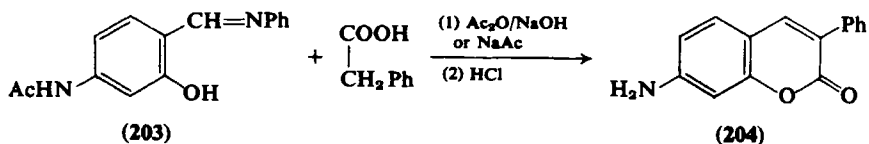


XII. Ring-Closure Reactions

A. COUMARINS, BENZO[*b*]-, AND NAPHTHO[2,1-*b*]furans

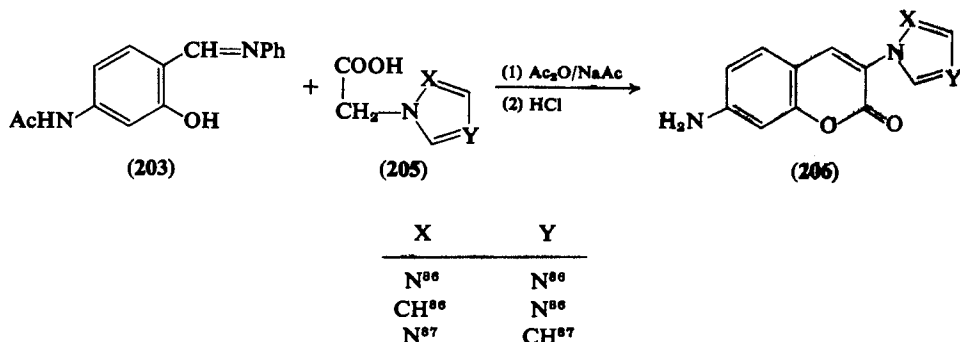
A number of examples have been reported in which methylene and methyl group-containing compounds react with Schiff's bases in such a way as to form cyclic systems.

Thus, reaction of the salicylidineaniline (**203**) with phenylacetic acid in the presence of acetic anhydride and either sodium hydroxide or acetate has been found to yield, following acid hydrolysis, 3-phenyl-7-aminocoumarin (**204**).⁸⁵

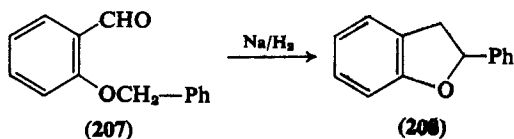


In the case of the parent acetylaminosalicylaldehyde, it was stated⁸⁵ that, under similar conditions, no 3-phenyl-7-aminocoumarin was obtained. Furthermore, this reaction has also been carried out with a number of heterocyclic acetic acids of general formula **205**, resulting in the formation of the various 3-heterocyclic-7-amino-substituted coumarins (**206**).

⁸⁵ C.-W. Schellhammer, K.-W. Mueller, and R. Raue (Bayer AG), U.S. Patent 3,352,885 (Ger. Appl. 1964).



The intramolecular ring closure of 2-benzyloxybenzaldehyde (**207**), as a preparative route to 2-phenylbenzo[*b*]furan, was first attempted in 1903.⁸⁸ However, the extremely drastic conditions of treatment with molten sodium under a hydrogen atmosphere led only to the formation, in poor yield, of the 2,3-dihydro derivative **208**.



In 1960 the reaction of 4-nitrobenzylbromide (**209**) with salicylaldehyde in the presence of potassium carbonate was reported to give an 80% yield of 2-(4-nitrophenyl)benzo[*b*]furan (**219**).⁸⁹ However, the analogous reaction of 4-chlorobenzylbromide (**211**) resulted only in the formation of 2-(4-chlorobenzyloxy)benzaldehyde (**212**).

It was later shown that a number of benzo[*b*]- and naphtho[2,1-*b*]-furans could be obtained by cyclization of the corresponding 1-formyl-2-(4-cyanobenzyloxy)benzenes in DMF in the presence of powdered potassium hydroxide, e.g., **213** → **214**.^{90,91}

⁸⁶ A. Dorlars, C.-W. Schellhammer, and W.-D. Wirth (Bayer AG), British Patent 1,201,759 (Ger. Appl. 1968).

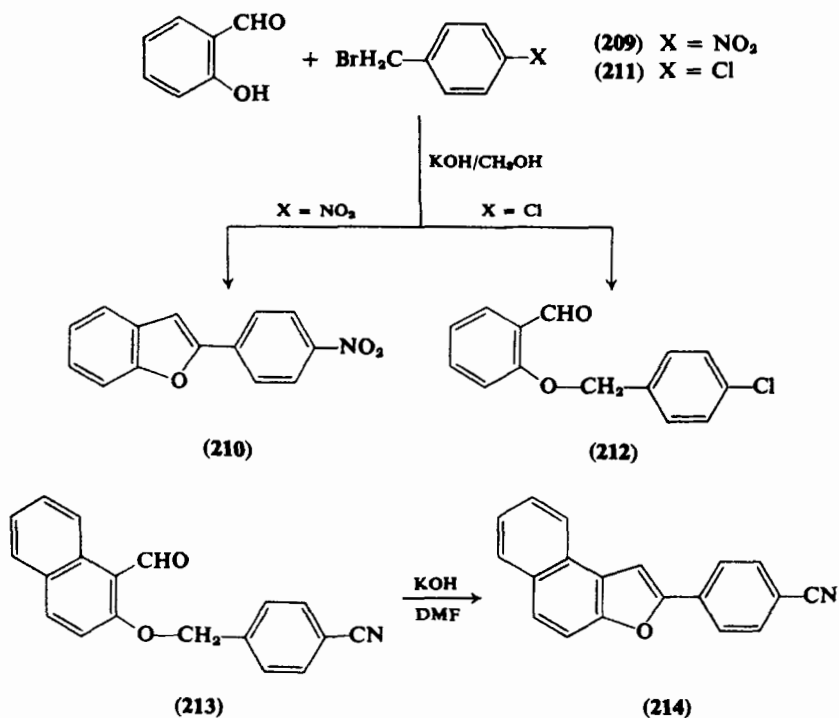
⁸⁷ W.-D. Wirth (Bayer AG), British Patent 1,104,537 (Ger. Appl. 1965).

⁸⁸ R. Stoermer, *Ber. Deut. Chem. Ges.* **36**, 3979 (1903).

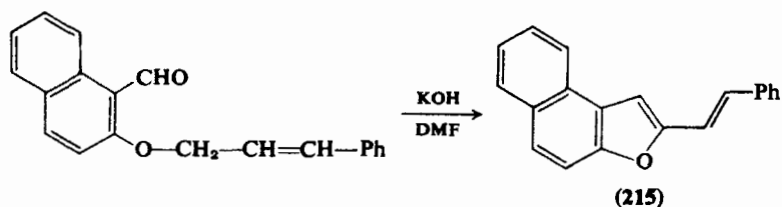
⁸⁹ K.B.L. Mathur and H. S. Mehra, *J. Chem. Soc.*, 1954 (1960).

⁹⁰ W. Sahm and G. Roesch (Hoechst AG), U.S. Patent 3,928,390 (Swiss. Appl. 1971).

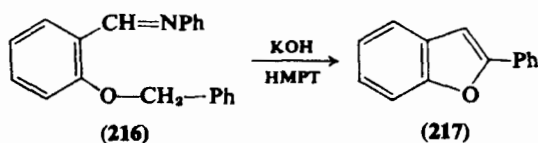
⁹¹ W. Sahm and A. Horn (Hoechst AG), U.S. Patent 3,864,333 (Swiss Appl. 1971).



That the presence of the nitrile group was not essential for cyclization was also demonstrated⁹¹ by the preparation of 2-styrylnaphthofuran (215).

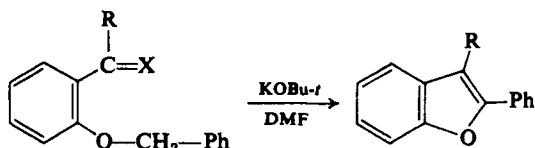


However, the analogous preparation of the parent 2-phenylbenzo[b]furan (217) was not reported until cyclization of Schiff's base 216, derived from 1-formyl-2-benzyloxybenzene and aniline, in the sense of



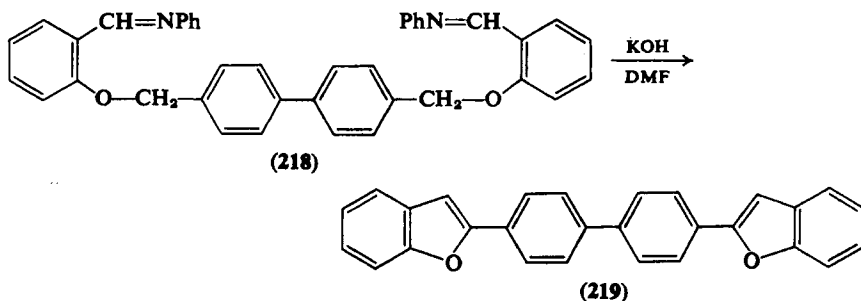
an intramolecular Anil Synthesis, was shown to be successful.⁹² A representative number of benzo[*b*]- and naphtho[2,1-*b*]furans prepared in this way are shown in Table XXI.

Despite the fact that a number of these products had previously been obtained^{90,91} by cyclization of the corresponding aldehydes, it was later stated¹² that the Schiff's base method is useful in cases where poor or negligible yields are obtained from the aldehydes, as exemplified by the following reaction:



R	X	Yield %
H	O	59
H	NPh	75
Me	O	0
Me	NPh	36

Further, the 4,4'-bisbenzofuranyl biphenyl (**219**) has been found¹² to be far more readily obtainable from the dianil **218** than from the

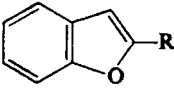
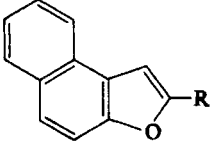
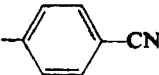

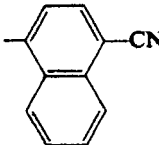
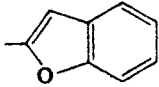
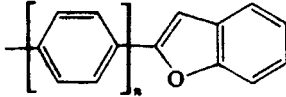
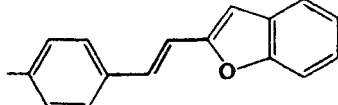
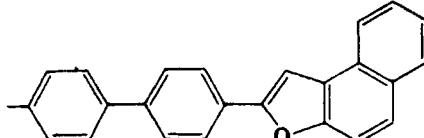
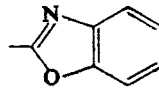
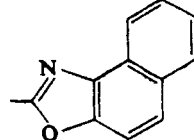


corresponding dialdehyde. Compounds such as **219** and others listed in Table XXI have been patented for use as fluorescent whitening agents.^{90,93}

⁹² W. Sahn (Hoechst AG), U.S. Patent 3,892,807 (Swiss Appl. 1972).

⁹³ W. Sahn, E. Schinzel, and G. Roesch (Hoechst AG), U.S. Patent 3,859,350 (Swiss Appl. 1971).

TABLE XXI: BENZO- AND NAPHTHOFURANS^a

Substituent R	 m.p. (°C)	 m.p. (°C)
	137-139	173-175
	124-125	176-177
	126-128	—
	197-198	171
	$\begin{cases} (n = 1) & 308-309 \\ (n = 2) & > 350 \end{cases}$	—
	290	—
	—	> 350
	—	170-172
	204	—

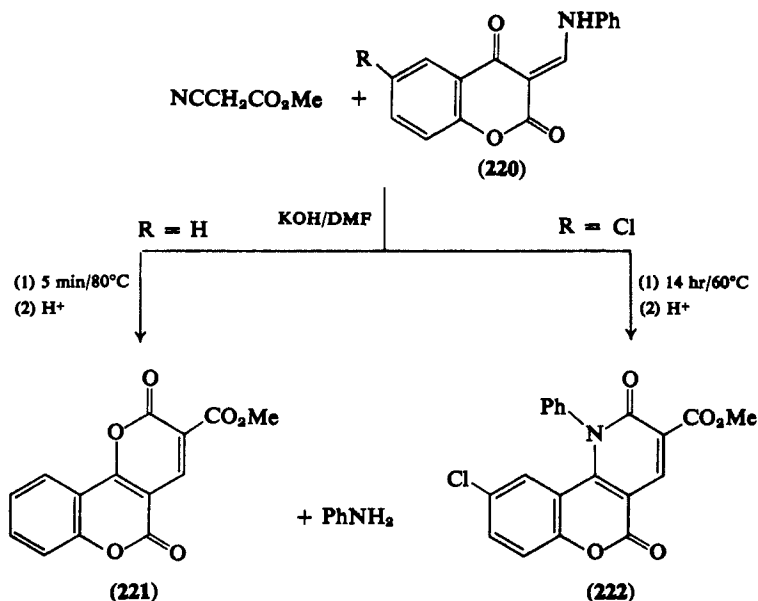
^a From Sahm (Ref. 92).

**B. PYRONOCOUMARINS, PYRONOQUINOLONES, AND
DIHYDROQUINOLINES**

A further use of anils in the synthesis of heterocyclic compounds has been observed¹⁴ in the synthesis of pyronocoumarins and pyrono-2-quinolones.

Thus, with methyl and also ethyl cyanoacetate, the anilinomethylene chromonedione (**220**) (this form has been found⁹⁴ to predominate in dimethylsulfoxide solution rather than the tautomeric structure of the formal Schiff's base from 3-formyl-4-hydroxycoumarin and aniline) yields, initially, with potassium hydroxide in DMF, following hydrolysis, the pyronocoumarin **221**.

However, extended reaction times have been found to result in reaction of the aniline formed with the pyronocoumarin, leading to formation of the pyridonocoumarin **222**. A similar reaction has been observed⁹⁵ in the hexahydrocoumarin series.

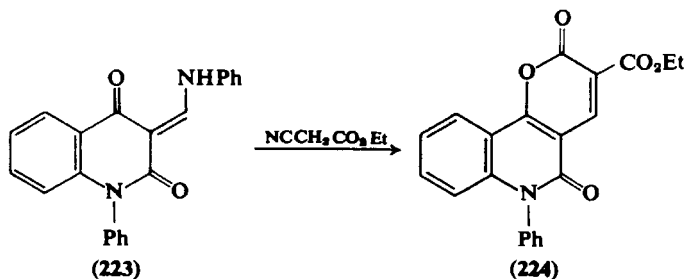


Reaction of **220** ($\text{R} = \text{H}$) with malononitrile leads directly to formation of the cyanopyridonocoumarin, whereas with *p*-nitrophenyl-acetonitrile reaction stops at the pyronocoumarin stage.

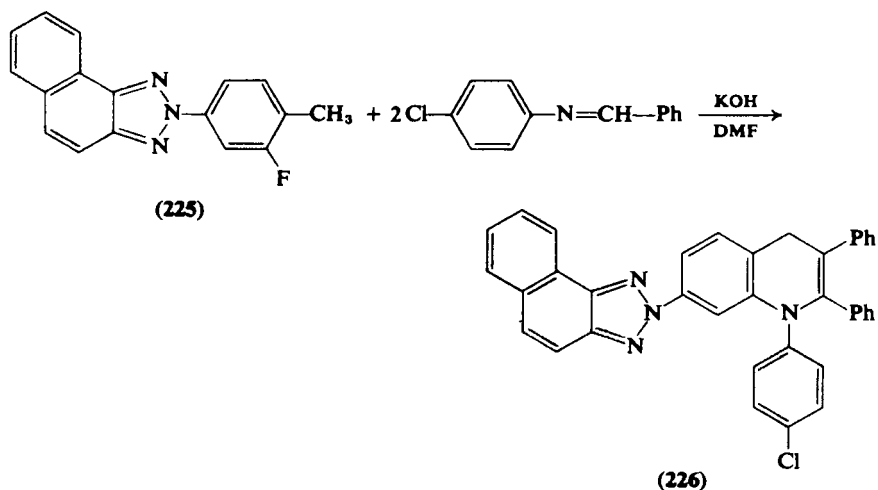
⁹⁴ P. Olliger, O.S. Wolfbeis, and H. Junek, *Montash. Chem.* **106**, 963 (1975).

⁹⁵ N. P. Shusherina, T. K. Gladysheva, and R. Y. Levina, *Vestn. Mosk. Univ., Khim.* **23**, 101 (1968) [*CA* **69**, 27191 (1968)].

It was further reported¹⁴ that anilinomethylenecarbostyrls can undergo similar reactions, as exemplified by the transformation **223** \rightarrow **224**.



On reaction of 2-(3-fluoro-4-methylphenyl)-2*H*-naphtho[1,2-*d*]triazole (**225**) with the Schiff's base from benzaldehyde and *p*-chloroaniline with potassium hydroxide in DMF, it has been reported⁶⁸ that, not the expected stilbene, but rather the dihydroquinoline **226** is formed. It was



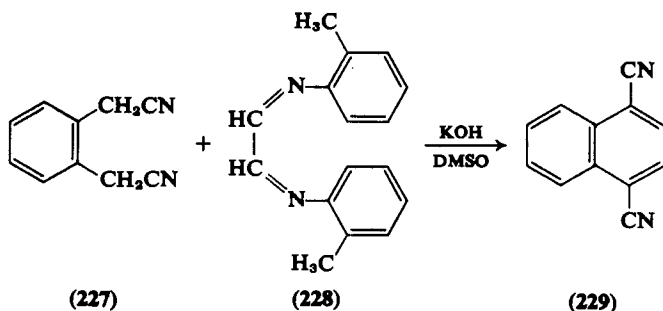
then observed that this reaction occurs with other Schiff's bases and also with *o*-fluorotoluene.⁶⁸

C. NAPHTHALENE AND CYCLOPROPANE DERIVATIVES

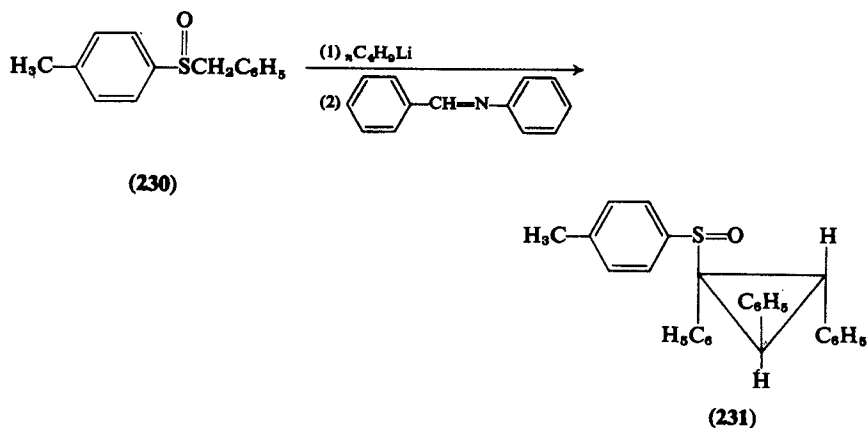
A similar reaction in the carbocyclic series for the preparation of 1,4-dicyanonaphthalene (**229**) has also been reported recently.⁹⁶ For

⁹⁶ H. Lorenz and K. Uhl (Hoechst AG), Ger. Pat. Publ. 2,503,321 (Ger. Appl. 1975).

example, *N*-*o*-toluidineglyoxalbisaldimine (**228**) reacts with *o*-phenylenediacetonitrile (**227**) in dimethyl sulfoxide in the presence of catalytic quantities of potassium hydroxide powder to give the naphthalene **229**.



Finally, and also in the carbocyclic series, Nudelman and Cram have shown that treatment of benzyl-*p*-tolylsulfoxide (**230**) with butyllithium and then with benzalaniline leads to the formation of the cyclopropane derivative **231**.⁹⁷



⁹⁷ A. Nudelman and D. J. Cram, *J. Org. Chem.* **34**, 3659 (1969).

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Reactions of Acetylenecarboxylic Esters with Nitrogen-Containing Heterocycles

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I. Introduction

A. REACTIONS OF ACETYLENIC ESTERS WITH HETEROCYCLES

Addition reactions of acetylenic acids and esters to nitrogen-containing heterocycles were reviewed in 1963 in the first volume of *Advances in Heterocyclic Chemistry*,¹ and the synthesis of heterocycles from acetylenic esters has been documented in Volume 19.² Since 1963 an enormous amount of new work concerning reactions of acetylenes with heterocycles has been reported, a few review articles dealing with limited areas have appeared,³⁻⁷ and nitrogen, oxygen, sulfur and a few other elements, alone or severally, have acted as heteroatoms. These investigations have been stimulated both by the problems involved in unravelling the novel types of structures sometimes produced and by

¹ R. M. Acheson, *Adv. Heterocycl. Chem.* **1**, 125 (1963).

² M. V. George, S. K. Khetan, and R. K. Gupta, *Adv. Heterocycl. Chem.* **19**, 279 (1976).

³ R. Huisgen, *Chem. Weekbl.* **59**, 89 (1963).

⁴ R. M. Acheson, *Khim. Geterosikl. Soedin.*, 1011 (1976).

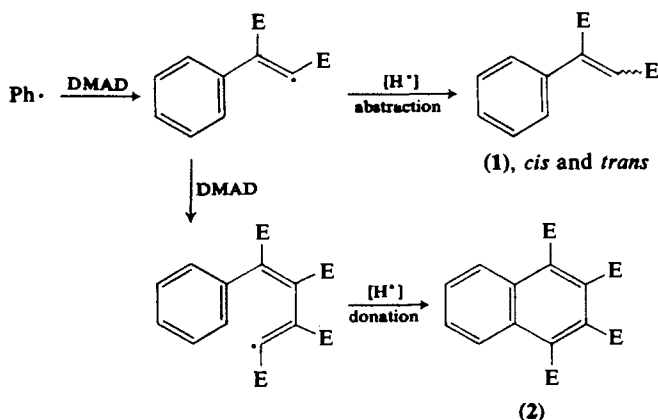
⁵ H. G. Viehe (ed.) "Chemistry of Acetylenes." Dekker, New York, 1969.

⁶ E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.* **6**, 423 (1967).

⁷ T. Uchida and K. Matsumoto, *Synthesis*, 209 (1976).

the great strides^{8,9} which have been made in the theories of concerted addition reactions. These theories enable predictions to be made of what might happen when particular reactants are treated with heat or light. Although it is difficult to predict clearly whether lone pairs of electrons present on heteroatoms will alter what might be expected from the behavior of analogous carbocycles, for instance when an N atom ($=\ddot{N}-$) replaces a methine group in one of the reactants, it appears that the availability of lone pairs does not alter the reaction courses in the cases examined. There is a current controversy concerning the concerted 1,3-dipolar¹⁰ or nonconcerted radical¹¹ nature of some cycloadditions between nitrogen-containing ylids with acetylenes and ethylenes; different pathways might well be taken by apparently closely similar reactions carried out under similar conditions. Some reactions of dimethyl acetylenedicarboxylate (DMAD), the corresponding diethyl ester (DEAD), methyl (MP) and ethyl propiolates (EP), and ethyl phenylpropiolate (EPP) take place with reasonable certainty through each of radical, ionic, and concerted pathways. Examples of each type are now given.

Phenyl radicals,¹² from dibenzoyl peroxide, with DMAD give a mixture of the *cis* and *trans* isomers **1** and the naphthalene **2**. (In all structures, E = ester, corresponding to the original ester used.)



⁸ R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry." Academic Press, New York, 1970.

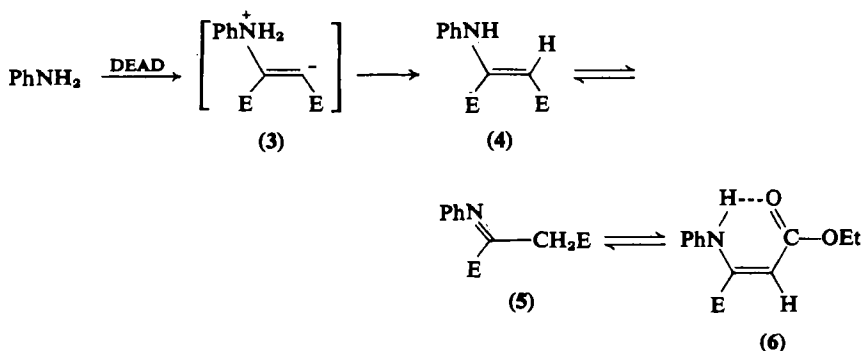
⁹ T. L. Gilchrist and R. C. Storr, "Organic Reactions and Orbital Symmetry." Cambridge Univ. Press, London and New York, 1972.

¹⁰ R. Huisgen, *J. Org. Chem.* **41**, 406 (1976).

¹¹ R. A. Firestone, *J. Org. Chem.* **37**, 2181 (1972).

¹² B. D. Baigrie, J. I. G. Cadogan, J. Cook, and J. T. Sharp, *Chem. Commun.*, 1318 (1972).

Primary and secondary amines with acetylenic esters almost invariably undergo Michael-type additions to the triple bond, in preference to amide formation from reaction at the ester group, with the production of mixtures of *cis* and *trans* isomers. The ratios of the isomers formed are very solvent-dependent, and it has been shown¹³ by NMR studies that, in the case of aniline, *cis* addition first occurs to give **4** which is presumably formed by intramolecular shift of a proton in the postulated intermediate **3**. Tautomerism of **4** subsequently gives **5**, detected by NMR, and then a further tautomeric change yields the hydrogen bonded **6**. This last compound is the sole product when methanol is employed as reaction medium¹⁴ and could also be formed directly from **3** by intermolecular protonation by the solvent.



Although there is no direct evidence for the postulated intermediate **3** in this example, there is evidence for the existence of analogous ylids in the aziridine series (see Section II, B), and in some reactions of pyridine-type heterocycles with DMAD intermediates corresponding to **3** have been trapped. The formation of intermediates similar to **3** is the commonest first stage in reactions of nitrogen-containing heterocycles with activated acetylenes.

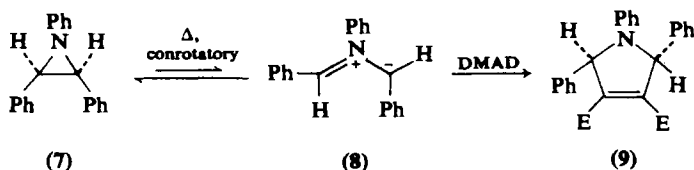
For many years¹⁵ activated acetylenes have been known to undergo Diels–Alder reactions, which take place^{8,9} by concerted processes. The stereochemistry of the pyrazoline **9**, obtained as sole product from the *cis*-aziridine **7** by heating in the presence of DMAD, can only be accounted for if opening of the ring to the ylid **8** is followed by a concerted, or extremely rapid, combination with the acetylene.¹⁶

¹³ S. Toppet, E. Van Lock, G. L'Abbé, and G. Smets, *Chem. Ind. (London)*, 703 (1971).

¹⁴ C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc. B*, 1217 (1966).

¹⁵ H. L. Holmes, *Org. React.* **4**, 60 (1948).

¹⁶ J. H. Hall, R. Huisgen, C. H. Ross, and W. S. Scheer, *Chem. Commun.*, 1188 (1971).



Reactions between nitrogen-containing heterocycles and acetylenic esters often lead to complex mixtures, which may require chromatography and great experimental skill for successful resolution. The products sometimes depend on the precise conditions employed, and on the purity of the reactants or solvents. The choice of solvent can be important. Thus ether and tetrahydrofuran give different results for the combination of DMAD with 1-methylbenzotriazole. The products obtainable from indoles and quinazolines are particularly dependent on the reaction conditions and purity of the solvent.

A further frequent complication is that acetylenic esters undergo base and acid-catalyzed self-condensation on standing under normal laboratory conditions, and they will add methanol or similar nucleophiles in Michael-type addition reactions (cf. 4 and 6). Such products are almost invariably present in reaction mixtures obtained from heterocycles. A short account of these products is included as their early recognition in a new investigation can save much time.

Although mechanisms have been advanced to account for the formation of the majority of the identified products from acetylenes and nitrogen-containing heterocycles, most are based on plausible analogies or on the trapping of an occasional postulated intermediate. Genuine mechanistic studies have been carried out for very few of the reactions noted in this review.

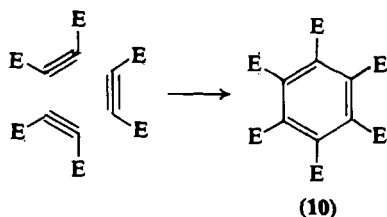
The main types of reaction between acetylenic esters and nitrogen-containing heterocycles up to 1962 have been summarized,¹ and as this summary is still essentially correct it will not be repeated. Further new types of reaction to which attention should particularly be drawn are described in Sections II,B, IV,G, V,A,3, V,C,2, V,G,2, V,M, and X,B.

B. SELF-CONDENSATION AND OTHER PRODUCTS FROM ACETYLENIC ESTERS

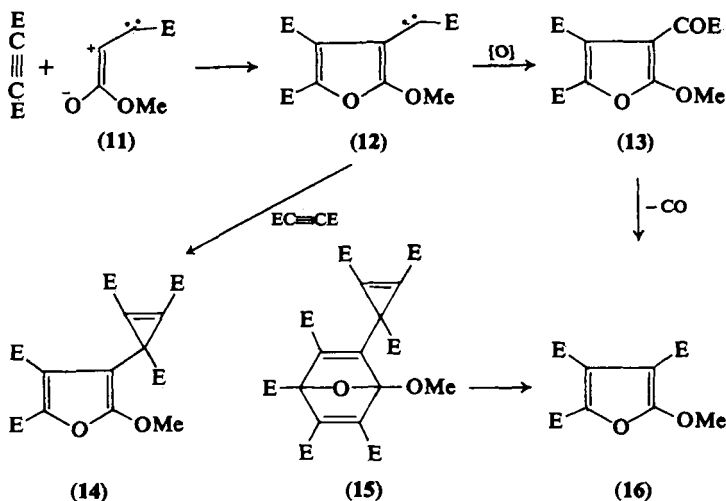
Dimethyl acetylenedicarboxylate combines with itself in several ways to give compounds which have been reported occasionally as unexplained products (e.g., 16)¹⁷ from reactions of the esters with other

¹⁷ C. F. Huebner, E. Donoghue, L. Dorfman, F. A. Stuber, N. Danieli, and E. Wenkert, *Tetrahedron Lett.*, 1185 (1966).

compounds. In the presence of tertiary amines, acids, perhaps best in acetic acid containing a trace of pyridine,¹⁸ trimerization gives hexamethyl mellitate or benzenehexacarboxylate (10).



Heating DMAD in the presence of oxygen (a trace of copper maximizes the yield) gives the furan 16. It is suggested that 1 mole of the acetylene combines with the carbenoid resonance form (11) to yield the carbene 12, which is converted by oxygen into the α -keto acid 13. Decarbonylation now gives the furan. Support for this scheme comes both from the detection of carbon monoxide¹⁹ as a product and the identification^{20,21} of the tetramer of DMAD as 15. The postulated carbene 12 with another mole of the acetylene could yield 14, which by a Diels-Alder addition across the 2,5-positions of the furan would give



¹⁸ O. Diels, K. Alder, T. Kashimoto, W. Friedrichsen, W. Eckhardt, and H. Klare, *Annalen* **498**, 16 (1932).

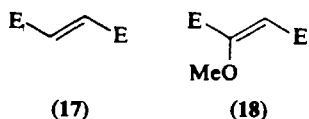
¹⁹ E. Winterfeldt and G. Giesler, *Angew. Chem., Int. Ed. Engl.* **5**, 579 (1966); *Chem. Ber.* **101**, 4022 (1968).

²⁰ E. LeGoff and R. B. LaCount, *Tetrahedron Lett.*, 2333 (1967).

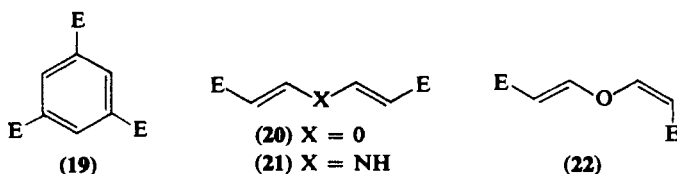
²¹ J. C. Sauer and H. E. Simmons, *J. Org. Chem.* **33**, 2720 (1968).

the desired compound. This tetramer (**15**) is formed²¹ at the rate of 3% per year by the pure monomer at 25°C, and up to a 25% conversion is obtained in 10 days at 85°C. Exclusion of light makes little difference to the polymerization although radical inhibitors such as hydroquinone slow it down. The tetramer exists in two crystalline forms, and a similar compound is formed from DEAD.²¹ Heating **15** causes a retro-Diels-Alder reaction leading to the furan **16**.

Other products commonly isolated from reactions of DMAD with heterocycles include dimethyl fumarate (**17**), the acetylene presumably acting as a dehydrogenating agent, and dimethyl methoxyfumarate (**18**).²² The latter could arise from the addition of methanol, present as an impurity, to the acetylene, or by nucleophilic attack on the carbonyl group of the acetylenic ester followed by expulsion of methoxide ion, which then undergoes a normal nucleophilic addition to the activated triple bond. It can be obtained, among other products, from the reaction of pyridine with DMAD in methanol.²³



Acetylenemonocarboxylic esters are more stable at ambient temperatures than the diesters but, nevertheless, the trimer, trimethyl trimesate (benzene-1,3,5-tricarboxylate) (**19**), has been isolated from reactions involving MP. Other products obtained from this acetylene in situations where water, or ammonia, can be produced are the geometric isomers **20** and **22**,²⁴ and the enamine **21**, respectively.²⁵ Methyl propiolate with water in benzene yields **20**.²⁶



²² R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 2676 (1964).

²³ O. Diels and K. Meyer, *Annalen* **513**, 129 (1934).

²⁴ R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 740 (1975).

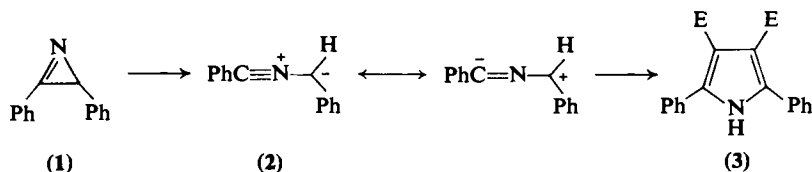
²⁵ R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 744 (1975).

²⁶ L. J. Kricka and J. M. Vernon, personal communication.

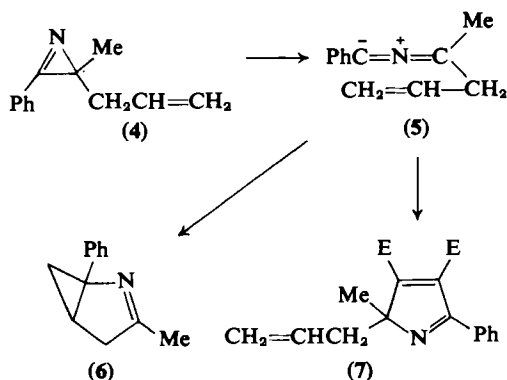
II. Three-Membered Ring Nitrogen-Containing Heterocycles

A. AZIRINES

Some cycloadditions to azirines have been reviewed by Anderson and Hassner.²⁷ Schmid *et al.*²⁸ photolyzed the arylazirine **1** in benzene in the presence of 2 equivalents of DMAD and obtained 40% of the pyrrole **3**, a compound prepared previously by Huisgen *et al.*^{29,30} from oxazolones and sydnone with DMAD. Padwa and his co-workers have investigated the scope of these photoinduced cycloadditions to arylazirines. Irradiation of **1** in pentane for 3 hours in the presence of DMAD gave 95% of (**3**)³¹; the azomethine ylid **2** was postulated as an intermediate.



Padwa and Carlsen³² photolyzed 3-allyl-3-methyl-2-phenylazirine (**4**) in the presence of excess DMAD and obtained the pyrrole **7** in high yield; in the absence of trapping agent, compound **6** was obtained. The interesting intermediate nitrilium betaine **5** was trapped by the



²⁷ D. J. Anderson and A. Hassner, *Synthesis*, 493 (1975).

²⁸ H. Giezendanner, M. Märky, B. Jackson, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **55**, 745 (1972).

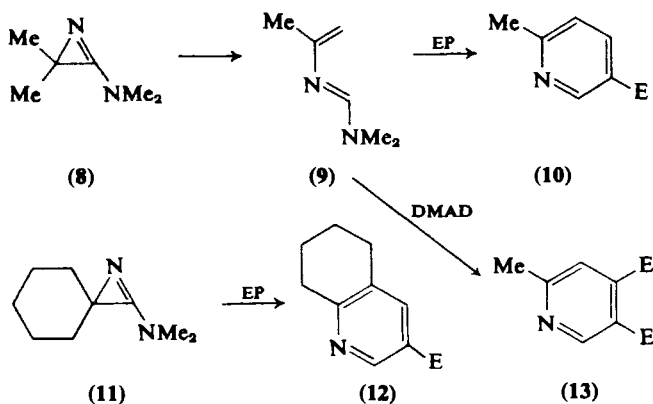
²⁹ R. Huisgen, H. Gotthardt, and H. O. Bayer, *Angew. Chem., Int. Ed. Engl.* **38**, 135 (1964).

³⁰ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Int. Ed. Engl.* **38**, 136 (1964).

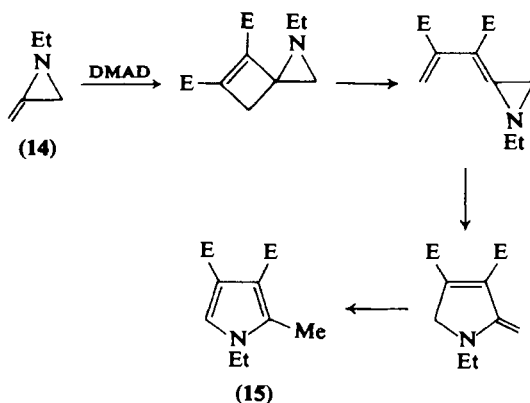
³¹ A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, *J. Am. Chem. Soc.* **95**, 1945 (1973).

³² A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.* **97**, 3862 (1975).

DMAD before carbenoid insertion leading to **6** took place. Thermolysis of 2-amino-1-azirines in the presence of acetylenic esters, for example heating **8** at 340° *in vacuo*, caused ring cleavage to the azadiene **9** which gave **10** with EP, and **13** with DMAD. A similar reaction between the spiroazirine **11** and EP gave **12**.³³



1-Ethyl-2-methyleneaziridine (**14**) with DMAD at room temperature gave³⁴ the pyrrole **15** (a mechanism is suggested in Scheme 1). Pyrrole **15** was unaffected by hot DMAD.



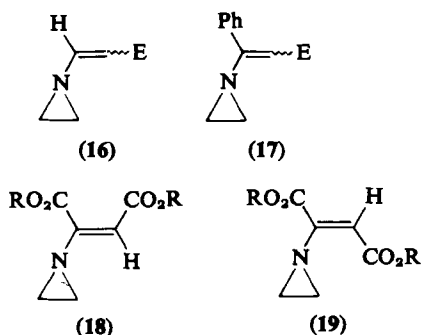
SCHEME 1

³³ A. Demoulin, H. Gorissen, A. M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.* **97**, 4409 (1975).

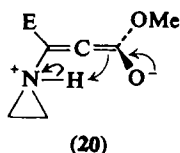
³⁴ R. C. Cookson, B. Halton, I. D. R. Stevens, and C. T. Watts, *J. Chem. Soc. C*, 928 (1967).

B. AZIRIDINES

Developments in aziridine chemistry, including the synthetic applications of their cycloadditions, have recently been reviewed by Lown and Matsumoto.³⁵⁻³⁷ Many investigators have added aziridines to acetylenic esters. Russian workers³⁸ treated aziridine in the cold with various esters and then heated the mixtures to 40°–60° for 3 hours. They obtained 59% of compound **16** with EP, and 71% of **17** with EPP, no stereochemistry being defined. Diethyl acetylenedicarboxylate gave 24% of the maleate **18** (R = Et) and 16% of the fumarate **19** (R = Et).



Dolfini³⁹ studied the stereospecificity of these additions. Combining equimolar quantities of aziridine and DMAD gave a 2:1 ratio of trans (**19**)/cis (**18**) adducts (R = Me) in 76% overall yield. The addition is solvent-dependent since in DMSO the ratio of **18** to **19** was 19:1. The author suggested that the zwitterion **20** was an intermediate in the aprotic solvent, reasoning that in the absence of a proton source, compound **20** would be expected to undergo stereospecific collapse via intramolecular protonation, leading to a cis orientation of the ester



³⁵ J. W. Lown, *Rec. Chem. Progr.* **32**, 51 (1971) [*CA* **76**, 3599 (1972)].

³⁶ M. Kiyoshi, *Kagaku No Ryoiki* **27**, 148 (1973) [*CA* **79**, 42,253 (1973)].

³⁷ J. W. Lown and K. Matsumoto, *Yuki Gosei Kagaku Kyokai Shi* **29**, 760 (1971) [*CA* **75**, 140,563 (1971)].

³⁸ I. Ya. Postovskii, E. I. Grinblat, and L. F. Trefilova, *Zh. Obshch. Khim.* **31**, 400 (1961) [*CA* **55**, 23,541 (1961)].

³⁹ J. E. Dolfini, *J. Org. Chem.* **30**, 1298 (1965).

functions; in protic solvents, protonation by the solvent could become the favored path. With EP, 85% of *trans*-**16** was obtained in dimethyl sulfoxide (DMSO), whereas in methanol a mixture containing 42% *trans*- and 58% *cis*-**16** was secured in 73% overall yield.

A complementary study⁴⁰ using a range of acetylenes provided similar results. For example, with EP in ethanol for 4 hours at room temperature, the proportions of *cis*:*trans* **16** were 46:54 in 81% yield; in benzene the ratio was 90:10 (80% yield).

Later, Huisgen *et al.*⁴¹ put forward a scheme which was similar to that of Dolfini. Their work indicated that both *cis* and *trans* adducts arose from the same intermediate, giving the *cis* adduct by internal proton shift, and both adducts, but mostly the *trans* compound, through the agency of external proton donors. Dolfini had shown that these adducts do not isomerize spontaneously below 80° and that the stability of the adducts to acid is high. In the NMR spectrometer the larger coupling constant for *trans* protons over *cis* protons provides a simple method for structure and product ratio determination.

The kinetics of the formation of compound **16** from EP and aziridine were measured by observing NMR spectral changes, a gradual decrease in the four proton aziridine signal being observed at 37°. The addition of DMAD to aziridine was studied by a UV technique. At the dilute concentrations used, in aprotic solvents, only *cis* adducts were found; the addition was second order.⁴²

Padwa and Hamilton examined other aziridines where the nitrogen was unsubstituted.^{43,44} *cis*-1,2-Diphenylaziridine (**21**) on refluxing with DMAD in benzene gave 85% of the adduct **22**; DEAD was also used. *trans*-2-Benzoyl-3-phenylaziridine (**23**) gave the pyrrole **24** with DMAD; the latter was also synthesized from 4-benzyl-2-phenyl-5-oxazolone (**26**), via **25**, which was oxidized with selenium dioxide to **24**.

When the aziridine nitrogen is substituted, Michael-type addition to the acetylene is not possible. Reactions are then usually preceded by ring cleavage with the formation of an azomethine ylid. The product obtained depends on the nitrogen substituent. Heine and co-workers^{45,46} used *cis*-1,2,3-triphenylaziridine (**27**) with DMAD, DEAD, EP, and EPP. The DMAD gave 98% of compound **28** after refluxing in toluene

⁴⁰ W. E. Truce and D. G. Brady, *J. Org. Chem.* **31**, 3543 (1966).

⁴¹ R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.*, 1883 (1967).

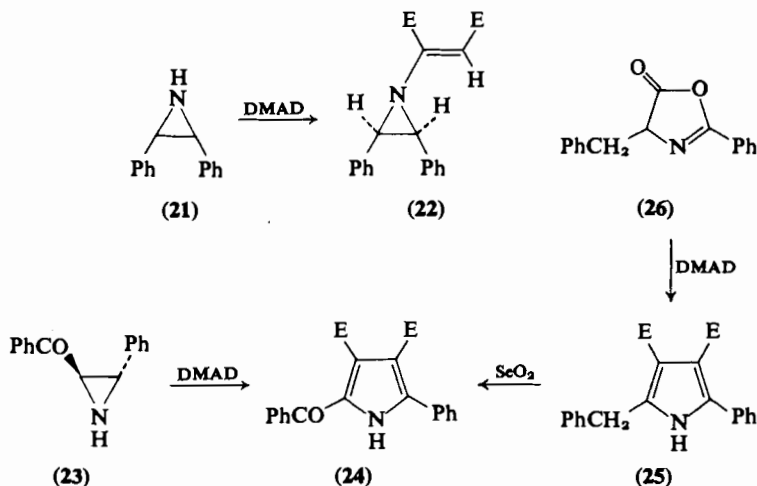
⁴² B. Giese and R. Huisgen, *Tetrahedron Lett.*, 1889 (1967).

⁴³ A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965).

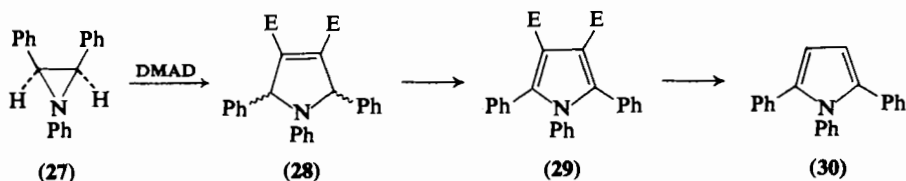
⁴⁴ A. Padwa and L. Hamilton, *J. Heterocycl. Chem.* **4**, 118 (1967).

⁴⁵ H. W. Heine and R. Peavy, *Tetrahedron Lett.*, 3123 (1965).

⁴⁶ H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.* **31**, 3924 (1966).



for 11 hours. The adduct was oxidized with chloranil to the pyrrole **29**, which was then hydrolyzed and decarboxylated to the known **30**.



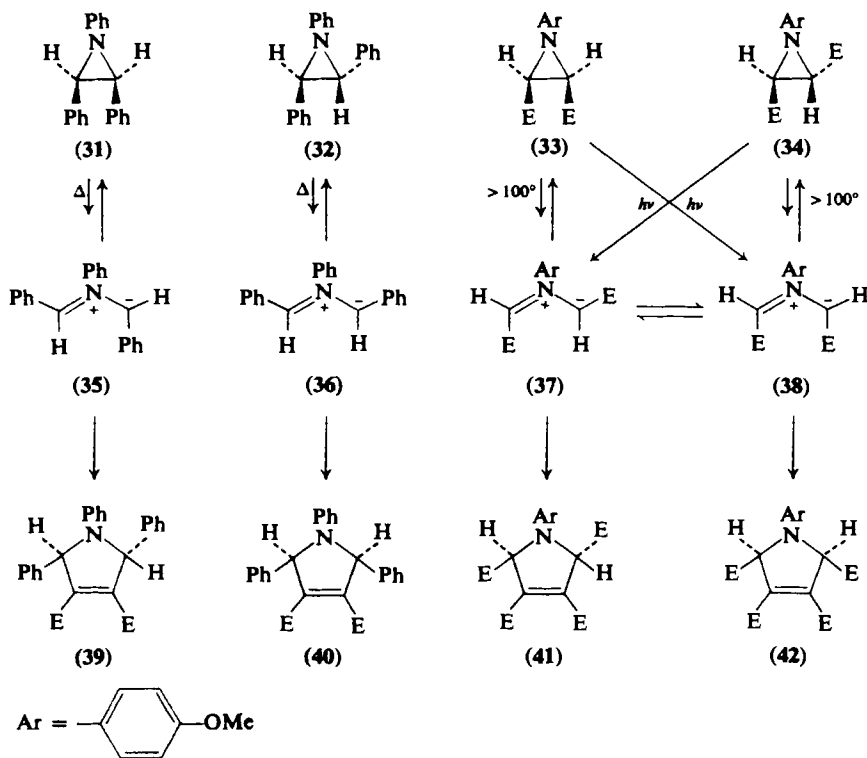
Huisgen's group¹⁶ demonstrated that at 150° *cis*-1,2,3-triphenylaziridine (**31**) equilibrated with the *trans* isomer (**32**) to form a 78:22 mixture. The azomethine ylids (**35**, **36**) were trapped with DMAD giving the pyrrolines (**39**, **40**) (Scheme 2). The assignments of structure were based on NMR interpretations. Woodward and Hoffmann⁴⁷ predicted that the thermal isomerization of the cyclopropyl anion to the allyl anion would proceed by a conrotatory ring opening, whereas a photochemical cleavage would take a disrotatory course. Aziridines are isoelectronic with cyclopropanes, and they behave similarly, the lone pair not getting involved, as shown by Huisgen's group.^{48,49} They separated the *cis* and *trans* isomers of dimethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate (**33**, **34**), studied their thermal and photochemical equilibria, and trapped the intermediate azomethine ylids (**37**, **38**) with DMAD. The cycloaddition of the dipolarophile competes with the equilibration

⁴⁷ R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965).

⁴⁸ R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.* **89**, 1753 (1967).

⁴⁹ R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.* **8**, 602 (1969).

process. Hence, *cis*-**33** was heated with 10 equivalents of DMAD for 14 hours at 100° and gave 98% of *trans*-pyrroline (**41**), which was oxidized with chloranil to a known pyrrole. Similarly, *trans*-aziridine (**34**) gave *cis*-pyrroline (**42**) in 71% yield. Irradiation of *trans*-aziridine (**34**) with neat DMAD as solvent (24 hours, 10°–15°) gave 40% of the *trans*-pyrroline (**41**); the yield was increased to 69% using 2% DMAD in dioxane. Irradiation of *cis*-aziridine (**33**) in DMAD as solvent caused no reaction, but with DMAD in dioxane both **41** and **42** were formed.



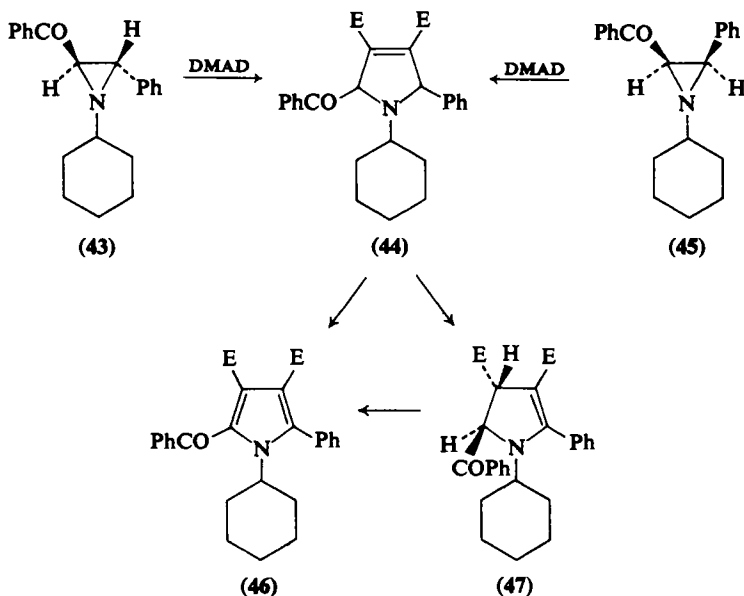
SCHEME 2

Differences in reactivity of compounds **37** and **38** became apparent when "weaker" dipolarophiles were used in the cycloaddition,⁵⁰ but DMAD is too reactive for this difference to become apparent.

Padwa and Hamilton's work⁴³ has been extended to the *N*-cyclohexyl derivatives (**43**, **45**). With these compounds the thermal addition of

⁵⁰ R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *Angew. Chem., Int. Ed. Engl.* **8**, 604 (1969).

DMAD led to compounds **46** and **47** in good yield. The pyrrole (**47**) was resistant to oxidation, and selenium dioxide in a sealed tube at 200° had to be used; the stability of **47** is a major reason for the structural assignment with the hydrogens in a *trans* relationship since the authors reason that a *cis* geometry would favor oxidation. The experimental data suggested that **46** did not come from **47** but was derived from the initially formed 3-pyrrole (**44**). These aziridines have also been



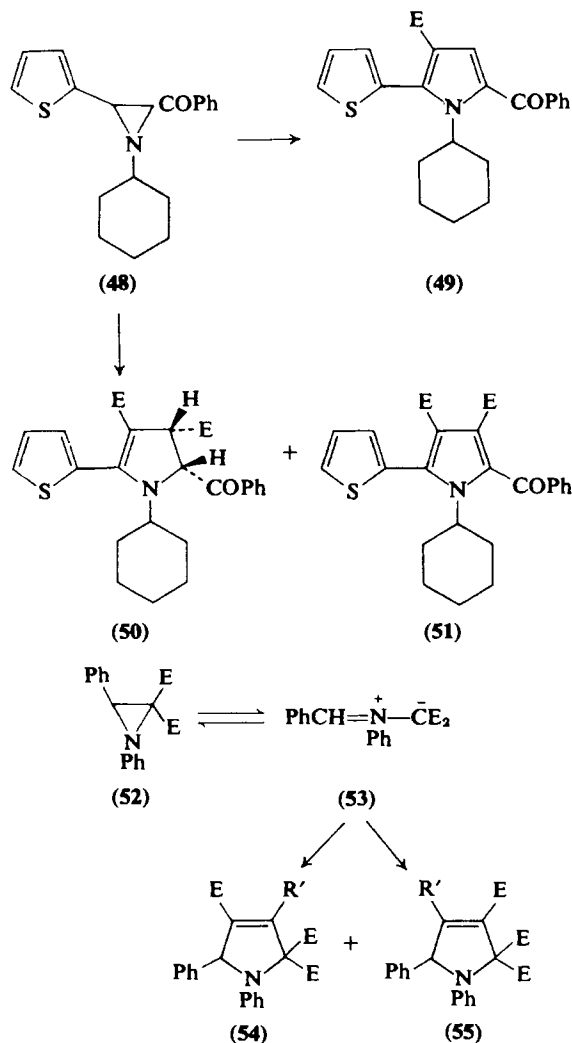
photolyzed, and the intermediate azomethine ylids were trapped with DMAD.⁴⁴

Lown and Matsumoto⁵¹ added DEAD and EP to the 2-(2'-thienyl)-aziridine **48** and obtained results similar to those described already. Hence *cis*- and *trans*-**48** with propiolic ester gave only the pyrrole **49**, whereas DMAD gave mostly compound **50** with some **51**.

The azomethine ylid **53**, generated thermally from the aziridine **52**, underwent cycloaddition in near quantitative yield. With DMAD, only one product is possible; with EP the sole product was **54**, and EPP gave **54** and **55** in 80:20 ratio. This latter result indicates that steric effects are important with the phenylpropionic ester.⁵² Nitrones (**57**) add to benzylideneacenaphthenone (**56**) forming the spiroisoxazolidines (**58**), which lose aldehyde fragments on heating or photolysis to give the

⁵¹ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **48**, 3399 (1970).

⁵² F. Texier and R. Carrié, *Bull. Soc. Chim. Fr.*, 2381 (1972).

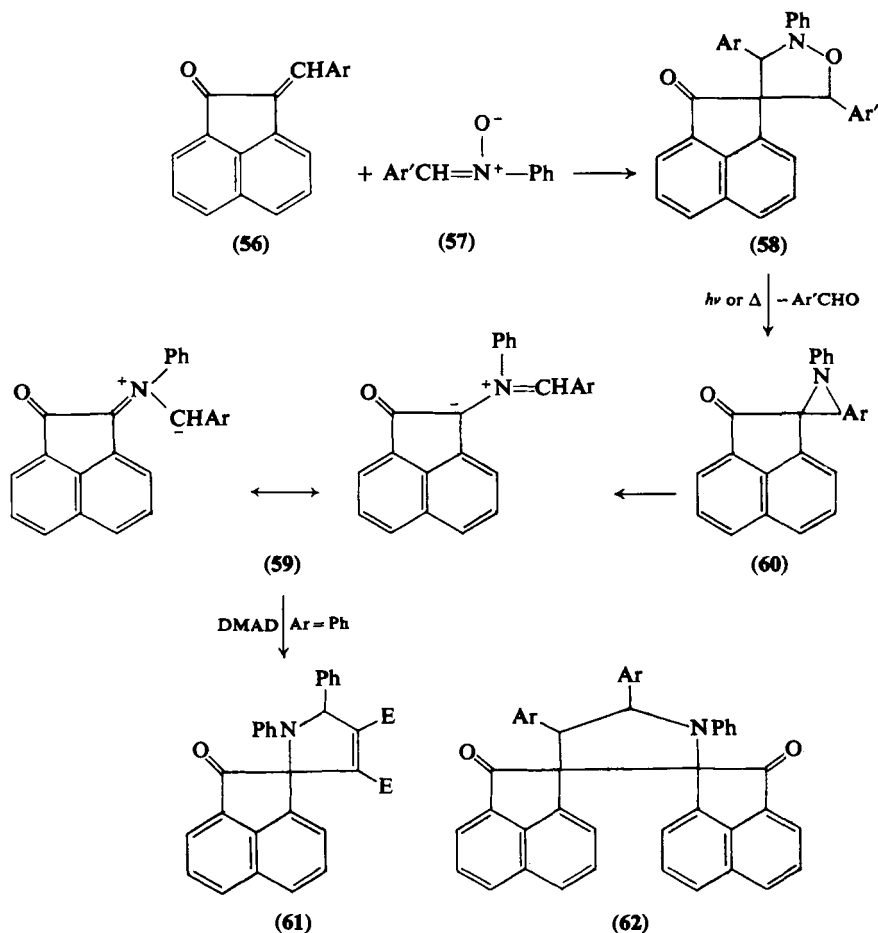


aziridines **60**.⁵³ These aziridines in hot xylene yield the azomethine ylids **59** that were trapped by DEAD giving compound **61** (29% yield) and the bisacenaphthenone **62** as by-products.⁵³

Thermal or photochemical decomposition of ethyl azidoformate in the presence of mesityl oxide gave the aziridine **63**, which thermolyzed in xylene to the 4-oxazoline **64**.⁵⁴ When **63** was heated with DMAD in

⁵³ O. Tsuge and I. Shinkai, *Tetrahedron Lett.*, 3847 (1970).

⁵⁴ T. Hiyama, H. Taguchi, and H. Nozaki, *Bull. Chem. Soc. Jpn.* **47**, 2909 (1974) [*CA* **82**, 86,253 (1975)].

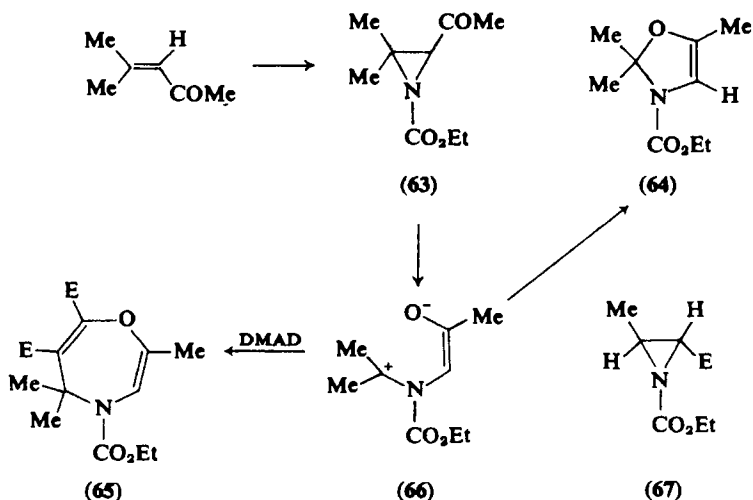


xylene, an 89% yield of the oxazepine **65** was obtained. The authors implicated the ylid **66** as an intermediate. The well-established mode of cycloaddition to azomethine ylids gives dihydropyrroles, as described above,⁵⁵⁻⁵⁷ but this type of compound was absent in this case. The difference is clearly due to the *N*-ester function as the other aziridines employed⁵⁴⁻⁵⁶ possess *N*-alkyl or *N*-aryl groups. Ester **67** was stable in hot xylene, but with DMAD it gave a low yield of an unidentified adduct.

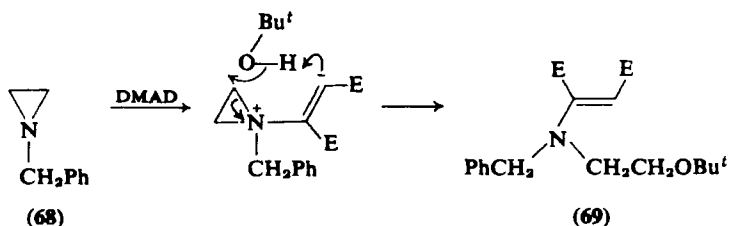
⁵⁵ J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *Chem. Commun.*, 1188 (1971).

⁵⁶ F. Texier and R. Carrié, *Tetrahedron Lett.*, 823 (1969).

⁵⁷ J. H. Hall and R. Huisgen, *Chem. Commun.*, 1187 (1967).



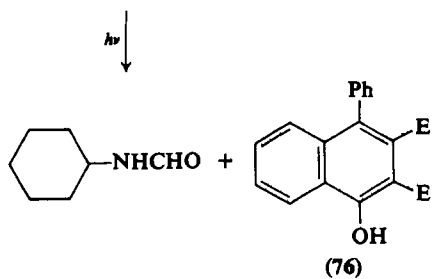
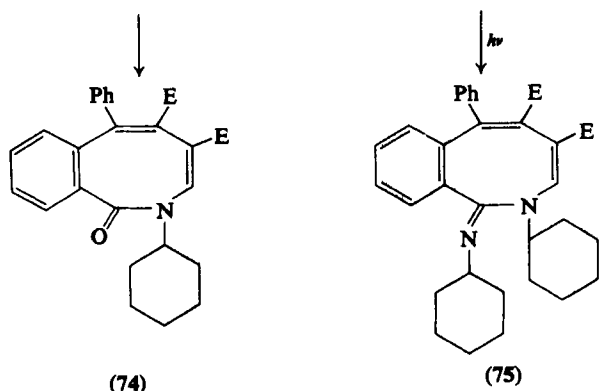
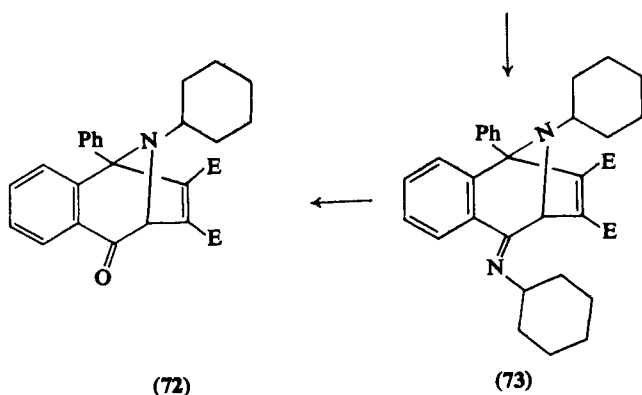
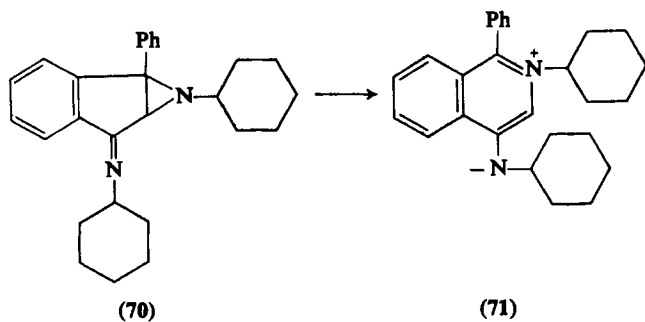
Winterfeldt and Dillinger⁵⁸ studied the addition of DEAD to *N*-benzylaziridine (68) in *t*-butanol and observed exclusive C—N bond cleavage, leading to compound 69. The reaction is surprisingly facile at room temperature and clearly does not proceed through an azomethine ylid. Interesting reactions take place when the aziridine is a part of a



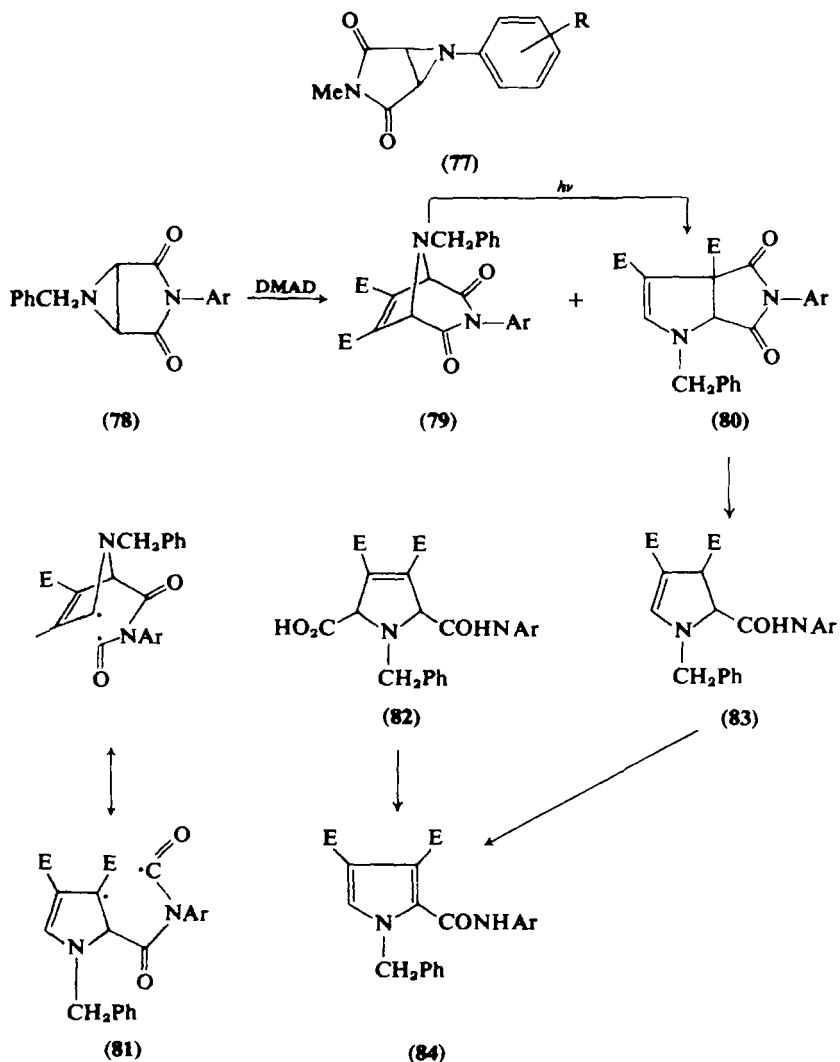
fused ring system. Recently, Padwa and Vega⁵⁹ found that heat or UV light partially converted 70 into the aromatic valence tautomer, the red isoquinolinium imine (71); the red color is discharged with oxygen, visible light, or acetylenes. The initial cycloadduct 73 formed in 71% yield by heating 70 for 36 hours with DMAD in xylene, underwent a novel rearrangement to a benzazocine (75) on photolysis. Mild acid hydrolysis of compound 73 gave 72 which, on heating, gave the benzazocine 74; photolysis of the latter gave the naphthol 76 and other products.

⁵⁸ E. Winterfeldt and H. J. Dillinger, *Chem. Ber.* **99**, 1558 (1966).

⁵⁹ A. Padwa and E. Vega, *J. Org. Chem.* **40**, 175 (1975).



Fusion of an aziridine moiety in a structure which cannot open in a conrotatory fashion inhibits the formation of an azomethine ylid by the thermal process. An example of such a compound is **77** which failed to give cycloadditions up to 180° .⁵⁰ Oida and Ohki⁶⁰ irradiated a related compound (**78**) in dioxane at 15° for 2 hours in the presence of 2 equivalents of DMAD. They obtained 4% of compound **79** and 36% of the isomeric **80**; mild alkaline hydrolysis of **79** gave the amorphous **82**,



Ar = *p*-MeOC₆H₄

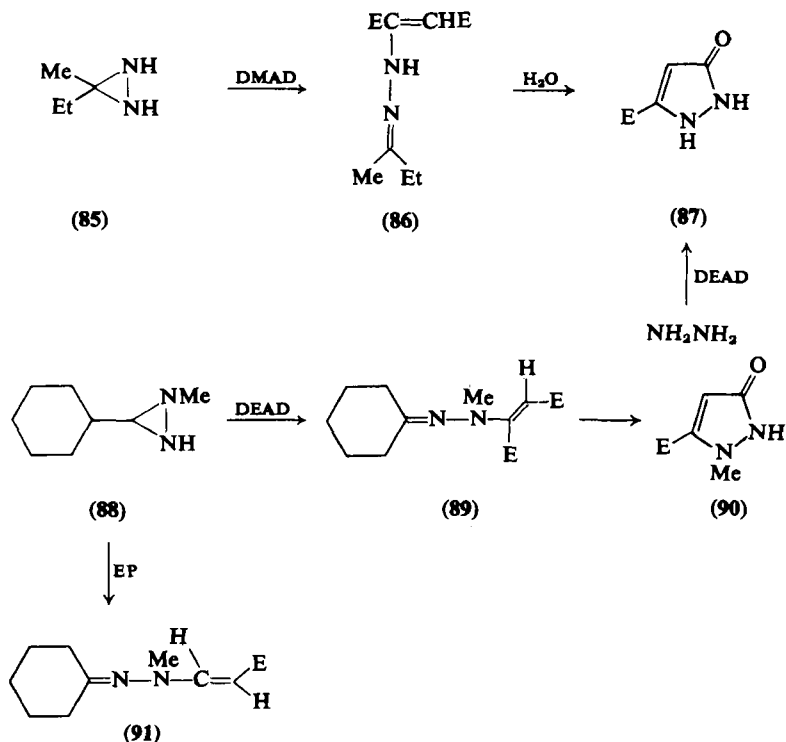
⁶⁰ J. Oida and E. Ohki, *Chem. Pharm. Bull.* **16**, 764 (1968).

which was oxidized to **84** in good yield. Spectroscopic techniques were used to assign the structure of **79**, which was totally resistant to oxidation with selenium dioxide. Formation of compound **80** was explained by rearrangement of the initially formed cycloadduct through the biradical intermediate **81**. Irradiation of **79** gave **80** and an unidentified product. In agreement with the orbital symmetry predictions mentioned earlier, heating **78** with DMAD at 100° did not give **79** or **80**; much starting material was recovered and an isolated 1:1 molar adduct could not be characterized.

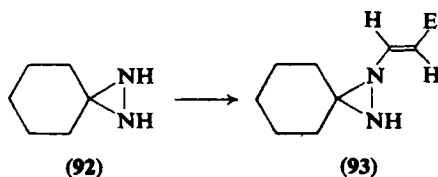
C. DIAZIRIDINES

The addition of 3,3-dialkyl-, 1,3-dialkyl-, and 1,3,3-trialkyldiaziridines to DEAD and EPP gives, generally, adducts in which the diaziridine ring is no longer intact.⁶¹

Diaziridines **85** and **88** gave oils with DEAD, presumably compounds **86** and **89**, which were hydrolyzed to the known pyrazolines **87** and **90**,



⁶¹ H. W. Heine, T. R. Hoye, P. G. Williard, and R. C. Hoye, *J. Org. Chem.* **28**, 2984 (1973).



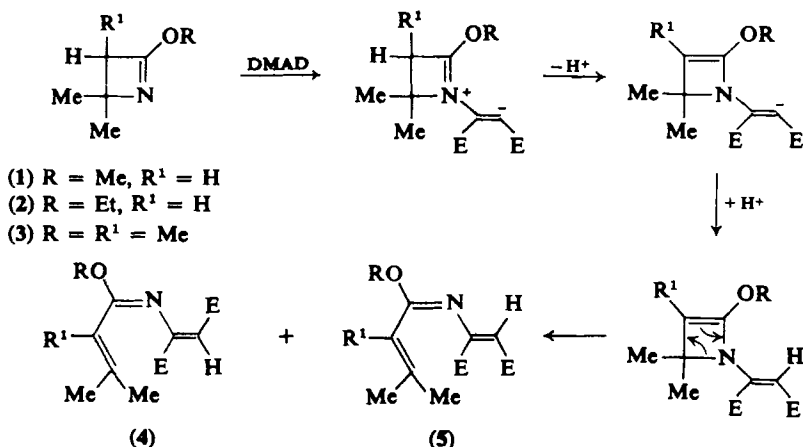
in turn prepared by the addition of hydrazine and methylhydrazine to DEAD. The addition of ethyl propiolate to **88** gave **91** with cleavage of the diaziridine ring; by contrast, the pentamethylene diaziridine **92** gave **93** with the heterocyclic ring intact.

III. Four-Membered Ring Nitrogen-Containing Heterocycles

A. AZETINES

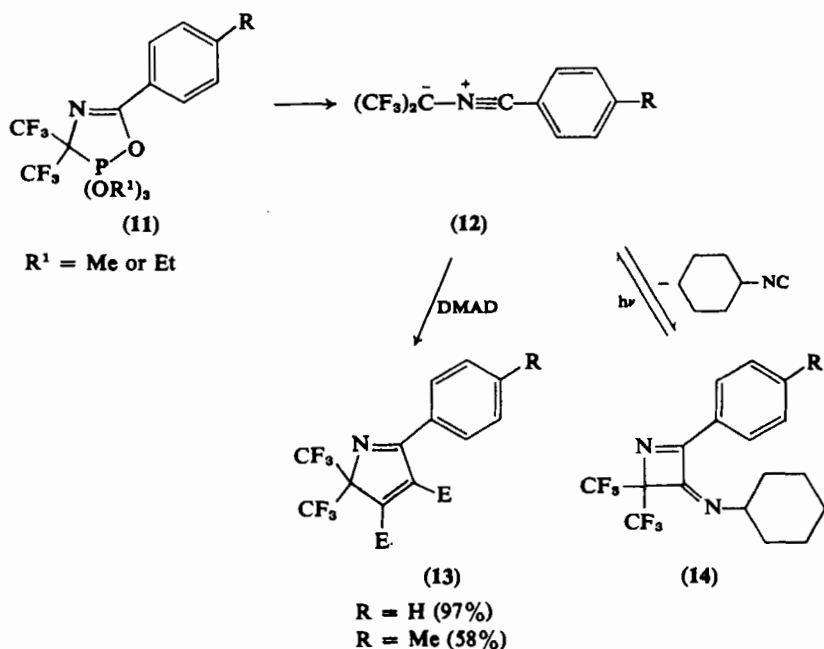
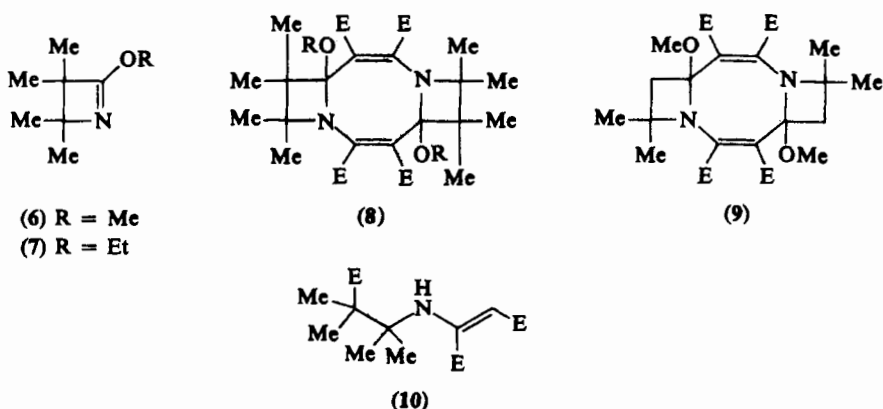
Aue and Thomas⁶² have described the addition of DMAD to a variety of imino ethers. The azetines **1** and **2** reacted readily in dichloromethane to give a 50:50 mixture of fumarate **4** and maleate esters **5** in greater than 50% yield.

The authors postulate the 1,3-dipolar intermediate shown. Analogously, the trimethylazetine **3** gave **4** ($R = R^1 = \text{CH}_3$) and **5** ($R = R^1 = \text{CH}_3$) in 26% total yield; the lower figure is almost certainly due to steric hindrance. There are no readily removable protons in the tetramethylazetine **6** so 1:1 adducts are not feasible. In dichloromethane



⁶² D. H. Aue and D. Thomas, *J. Org. Chem.* **40**, 2360 (1975).

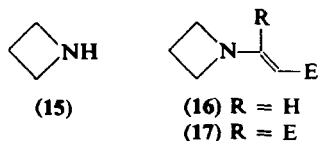
compound **6** gave polymers with DMAD, but in carbon tetrachloride an 88% yield of **8** (R = Et) was obtained from **7**; this remarkable solvent effect was explained by a difference in polarity. When the azetine **1** was treated with DMAD in carbon tetrachloride, a 2:2 molar adduct (**9**) resulted. Another interesting result was obtained by heating the tetramethylazetine **6** with DMAD in aqueous dioxane; the product was the amino ester **10**.



When 4,5-dihydro-1,3,5- λ^5 -oxazaphospholes (**11**)⁶³ are heated, nitrile ylids (**12**) are obtained.⁶⁴ The (3 + 1) cycloaddition of the latter to isocyanides leads to azetines (**14**), which, on photolysis in benzene, revert to the ylids (**12**); these intermediates have been trapped with DMAD⁶⁵ giving compound **13**.

B. AZETIDINES

The addition of azetidine (**15**) to DMAD proceeded exothermically to give dimethyl (1-azetidiny)lmalate (**17**) as a crystalline solid⁶⁶; with MP, compound **16** was obtained, and the NMR spectrum of this compound was informative of the stereochemical course of the reaction, which is solvent-dependent. In aprotic solvents, only *cis* addition occurred, giving the *trans*-acrylate, whereas in methanol a mixture of *cis* and *trans* products in the ratio 2:1 was obtained. The effect of solvents on the stereospecificity of the addition reaction agrees with that usually observed for secondary amines⁶⁷ but contrasts with aziridine where the *trans* addition competes to some degree with the *cis* addition even in aprotic solvents,^{39,68}



IV. Five-Membered Rings Containing Only Nitrogen as Heteroatom

A. PYRROLES

1. Compounds from Pyrroles and Alkylpyrroles

Pyrroles with or without an N substituent react at free α and β positions with DMAD yielding mixtures of the corresponding maleic and fumaric acid derivatives,⁶⁹ but other reactions also occur (see below).

⁶³ K. Burger, J. Fehn, and E. Moll, *Chem. Ber.* **104**, 1826 (1971).

⁶⁴ K. Burger and J. Fehn, *Chem. Ber.* **105**, 3814 (1972).

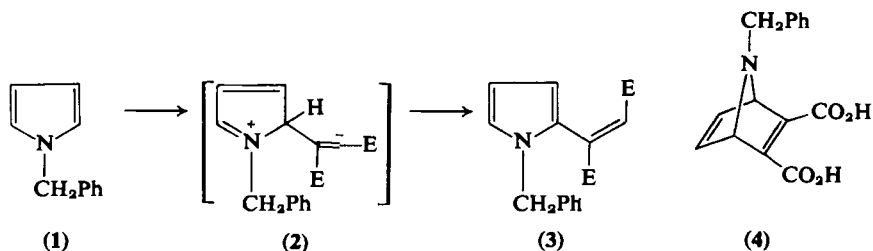
⁶⁵ K. Burger, W. Thenn, and E. Mueller, *Angew. Chem., Int. Ed. Engl.* **12**, 155 (1973).

⁶⁶ T. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.* **39**, 1618 (1966); **40**, 1964 (1967).

⁶⁷ R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.* **99**, 2526 (1966).

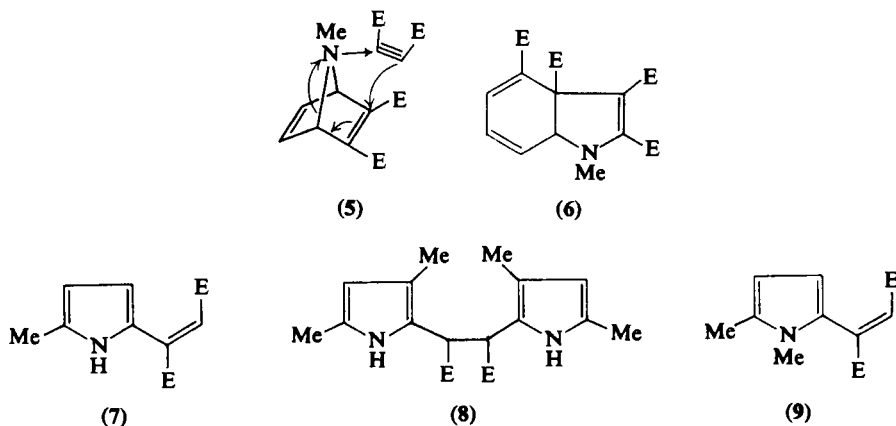
⁶⁸ E. Winterfeldt and H. Preuss, *Angew. Chem., Int. Ed. Engl.* **77**, 679 (1965).

⁶⁹ L. Mandell and W. E. Blanchard, *J. Am. Chem. Soc.* **79**, 6198 (1957).



A small number of pyrroles undergo addition of acetylenedicarboxylic acid across the 2,5 positions, yielding adducts similar to those derived from cyclopentadiene. For instance, 1-benzylpyrrole (1) gives some 4,^{69,70} but it is not known if the product is formed via a species such as 2 or by a concerted addition.

Dimethyl acetylenedicarboxylate and 1-methylpyrrole combine yielding mainly the dihydroindole 6. This is readily explained by assuming that the adduct 5 is first formed and that it then combines with a second molecule of the ester as indicated.⁷¹ This reaction has already been reviewed,¹ and, although attempts to isolate compound 5 have failed, a corresponding compound in the isoindole series¹⁹² has been obtained and gives the appropriate analog of 6 with more of the acetylenic ester.



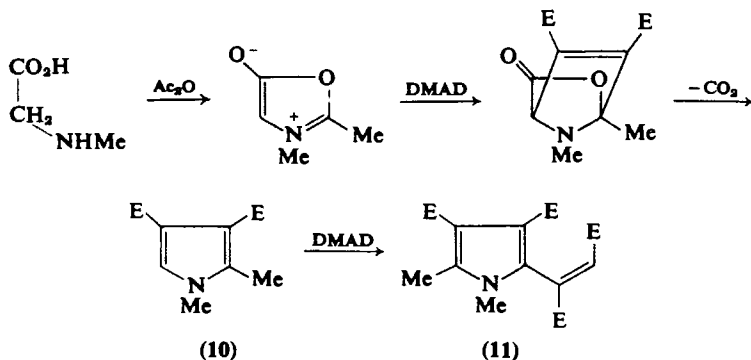
Dimethyl acetylenedicarboxylate with 2-methylpyrrole gives two 1:1 molar adducts, both of which on hydrogenation absorbed 1 mole of hydrogen and gave the same product.⁷² The original adducts are, therefore, dimethyl 2-methyl-5-pyrrolylfumarate (7) and maleate, but

⁷⁰ A. Shafi'ee and G. Hite, *J. Org. Chem.* **33**, 3435 (1968).

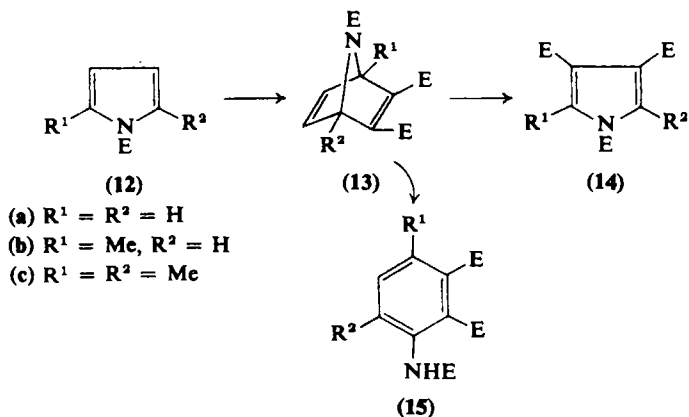
⁷¹ R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

⁷² O. Diels, K. Alder, H. Winckler, and E. Petersen, *Annalen* **498**, 1 (1932).

which is which was not established. A similar situation refers to 2,3-dimethylpyrrole, but only one adduct was obtained from 2,3,4-trimethylpyrrole.⁷² 2,4-Dimethylpyrrole and DMAD gave⁷³ a product analyzing for the bis-Michael adduct **8**, whereas 1,2-dimethylpyrrole and the ester gave⁷⁴ **9**. Addition of DMAD to sarcosine in the presence of acetic anhydride gave a mixture of the pyrrole **10** and its 1:1 molar adduct with DMAD (**11**), which were probably formed as shown.



Acheson and Vernon,⁷⁵ and later Gabel,⁷⁶ studied reactions of methyl pyrrole-1-carboxylates (**12a**) with DMAD. They obtained the pyrroles **14** and identified the acetylene formed, but were unable to isolate the proposed intermediates, azabicyclo[2,2,1]hepta-2,5-dienes (**13**). The



⁷³ O. Diels, K. Alder, and H. Winckler, *Annalen* **490**, 267 (1931).

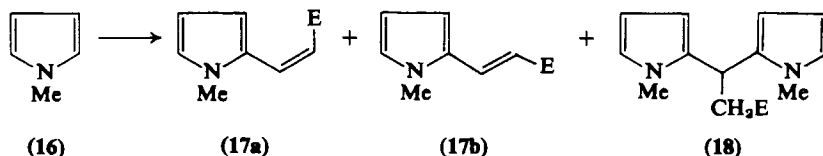
⁷⁴ R. M. Acheson, A. O. Plunkett, and J. M. Vernon, unpublished data.

⁷⁵ R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 457 (1961).

⁷⁶ N. W. Gabel, *J. Org. Chem.* **27**, 301 (1972).

highest yield (51%) was obtained with the 2,5-dimethyl derivative **12c** where α substitution was blocked. Methyl 2,5-diphenyl-1-pyrrole-carboxylate failed to react, steric hindrance probably having prevented combination.

Later Bansal, McCulloch, and McInnes^{77,78} found that the pyrroles **12** in benzene with DMAD for 7 days gave the azabicycloheptadienes **13** which on heating to 40° isomerized to the phthalates **15**. Most interestingly, the formation of **13** was accelerated by Lewis acids. With 5 equivalents of aluminum chloride, 50% of **13b** and 85% of **13c** were obtained in 30 minutes at 0° from the acetylenic ester and the pyrrole in dichloromethane. Compounds **15a** and **b** can be obtained in a one-vessel procedure comprising aluminum chloride-catalyzed cycloaddition at 0° followed by an *in situ* rearrangement at 40°, or, indirectly, by first isolating the adducts and then rearranging them. The aromatization of **13c** is difficult and can only be carried out by the two-step procedure. The aluminum chloride-catalyzed reaction of EP with *N*-methylpyrrole (**16**) gave adducts **17a** and **b** and **18**.⁷⁹



Thermal addition (105°–142°) of DMAD to other *N*-substituted pyrroles (**19a–d**)^{80–83} gave azabicycloheptadienes (**20**) in yields of 30–45%; lower temperatures sufficed for **19e–h**. The reversibility of the addition was demonstrated for **20f**, 60% of which after 9 hours at 65° in carbon tetrachloride was converted back into **19f**; compound **20h**, however, was unaffected. The azabicycloheptadiene **20** (R = CO₂Et) undergoes cycloaddition with 1 mole of 2,4,6-trimethylbenzonitrile oxide at both double bonds to give **26** and **27**, and both these products

⁷⁷ R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.* **47**, 2391 (1969).

⁷⁸ R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.* **48**, 1472 (1970).

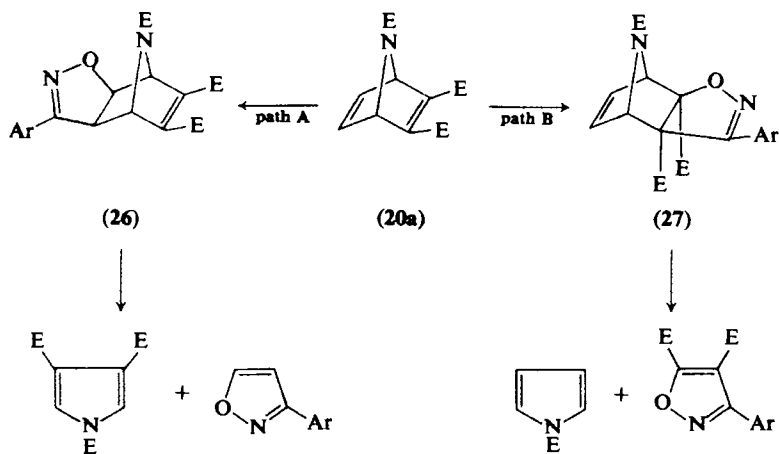
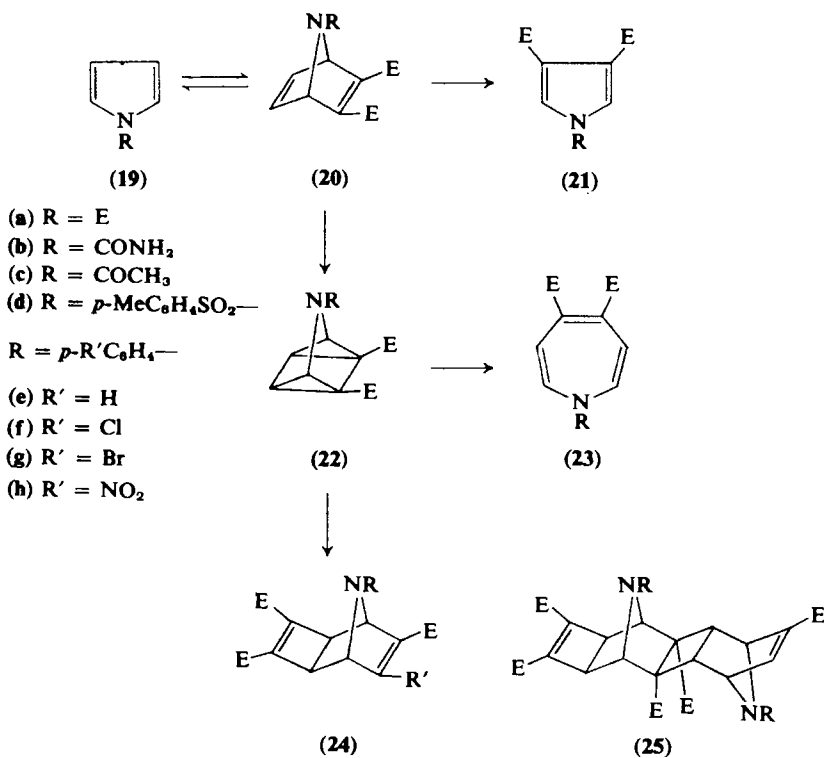
⁷⁹ A. W. McCulloch and A. G. McInnes, *Chem. Can.* **19**, 51,77 (1967) [*CA* **68**, 59,202 (1968)].

⁸⁰ H. Prinzbach, R. Fuchs, and R. Kitzing, *Angew. Chem., Int. Ed. Engl.* **7**, 67 (1968).

⁸¹ H. Prinzbach, R. Fuchs, R. Kitzing, and H. Achenbach, *Angew. Chem., Int. Ed. Engl.* **7**, 727 (1968); H. Prinzbach and W. Eberbach, *Chimia* **21**, 588 (1967).

⁸² R. Kitzing, R. Fuchs, M. Joyeux, and H. Prinzbach, *Helv. Chim. Acta* **51**, 888 (1968).

⁸³ H. Prinzbach, G. Kaupp, R. Fuchs, M. Joyeux, R. Kitzing, and J. Markert, *Chem. Ber.* **106**, 3824 (1973).

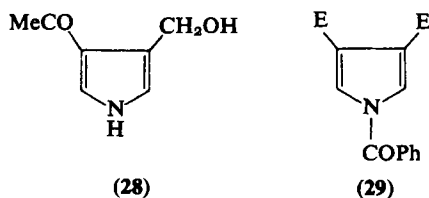


underwent thermal retro-Diels–Alder reactions to give the appropriate pyrroles and isoxazoles.⁸⁴

Photolysis (> 290 nm) induced quantitative conversion of (**20c** and **d**) to the crystalline 3-azaquadricyclanes (**22c** and **d**) that isomerize in solution at 20° to the azepines (**23c** and **d**) at measurable rates. The azepines rapidly dimerize. The “thermally forbidden”⁴⁷ reversal of **22** to **20** was not observed.⁸⁰ Prinzbach and Eberbach⁸¹ have carried out numerous cycloadditions and acid-catalyzed rearrangements of **22c** and **d** and of **23c** and **d**. The 3-azaquadricyclanes **22** have diene properties but, as valence isomerization to azepines is so easy (above), cycloadditions were achieved only with the very reactive dienophiles DMAD and EP. Reactions with **22c** and **d** at -15° to -30° over 24 to 48 hours using a large excess of ester gave **24** ($R' = H$ or E). If equimolecular proportions of the quadricyclane and ester are used, the products (**24**) compete as dienophile; for example, **24d** ($R' = H$) added to **20d** to give **25**.⁸¹

Gandhi and Chadha⁸⁵ have reported that the photolysis of pyrrole on DMAD by “unfiltered light” in the presence or absence of benzophenone gave **23** ($R = H$); the 3*H*-tautomer is a more probable formulation. In the presence of air, an adduct of DMAD with oxygen was obtained.

Anderson and co-workers⁸⁶ used the cycloaddition of acetylenic esters to **19a** and **19** ($R = \text{COPh}$) in the synthesis of the antimitotic agent Verrucaric acid (**28**). The pyrrole **19a** and DMAD gave 35% of **21a**, whereas **19** ($R = \text{COPh}$) gave 67% of **21** ($R = \text{COPh}$) and 23% of recovered starting material; 1-benzoylpyrrole gave 54% of **29** with DEAD. Further transformations produced the natural product.



The azabicyclohexene **30** (from **19a** and diazomethane) and the ethoxycarbonyl derivative **31** with DMAD at 100° gave the 8-azabicyclo[3,2,1]octenes **33** and **34**. The authors^{87,88} postulate that the

⁸⁴ D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron Lett.*, 2163 (1974).

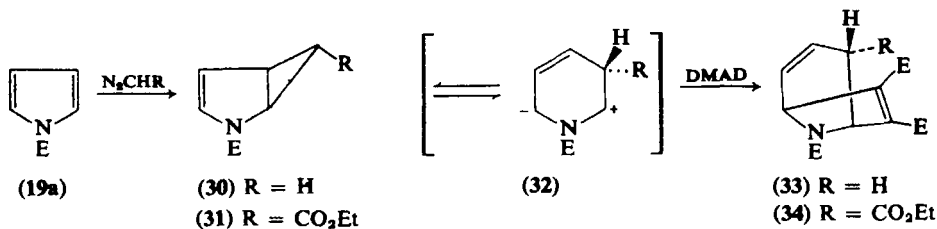
⁸⁵ R. P. Gandhi and V. K. Chadha, *Indian J. Chem.*, **9**, 305 (1971); [*CA* **75**, 48,881 (1971)].

⁸⁶ J. K. Groves, N. E. Cundaswamy, and H. J. Anderson, *Can. J. Chem.*, **51**, 1089 (1973).

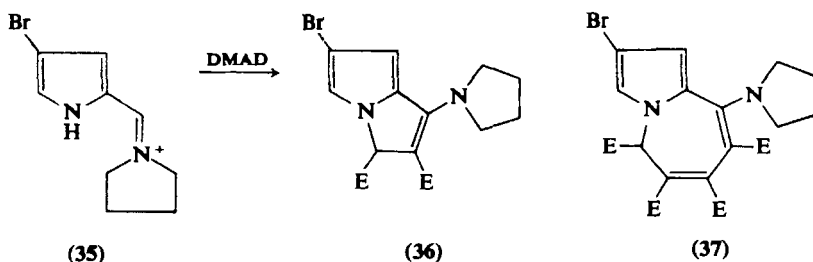
⁸⁷ F. W. Fowler, *Angew. Chem., Int. Ed. Engl.*, **10**, 135 (1971).

⁸⁸ S. R. Tanny and F. W. Fowler, *J. Org. Chem.*, **39**, 2715 (1974).

substrates (30, 31) may be in rapid equilibrium with a dipolar structure (32) which actually undergoes the cycloaddition.

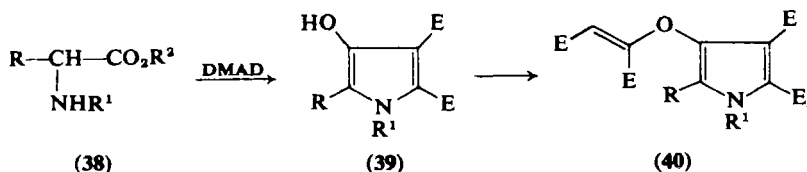


Sonnet, Flippen, and Gilardi⁸⁹ prepared the iminium salt 35 from 4-bromopyrrole-2-aldehyde; with DMAD it gave a 1:1 molar adduct (36) (38%) whose structure was determined by an X-ray crystallographic analysis, and a 1:2 adduct (37) (43%).



2. Compounds from 3-Oxy- and 3-Oxopyrroles

Amino acid derivatives (38) add DMAD to give hydroxypyrroles (39), which react further to give adducts (40).⁹⁰

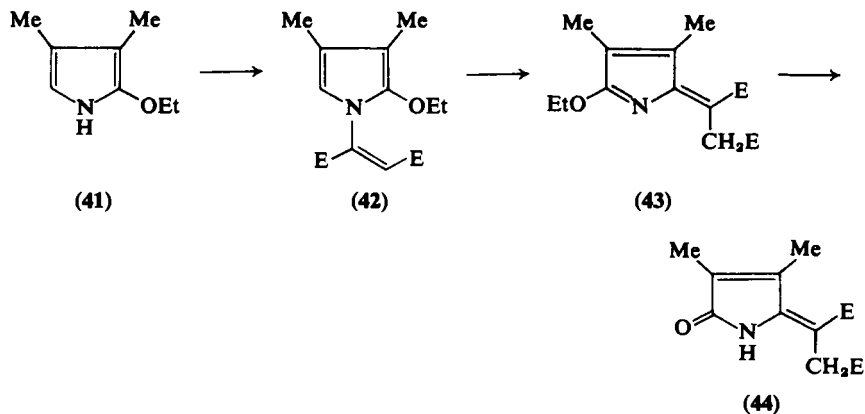


With the 2-ethoxypyrrole 41 at -70° , DMAD gave an 83% yield of 42; on warming to room temperature, the side chain migrated to the vacant α position to form 43, which was hydrolyzed to 44.⁹¹

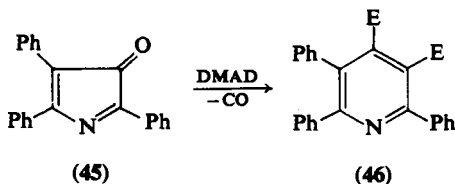
⁸⁹ P. E. Sonnet, J. L. Flippen, and R. N. Gilardi, *J. Heterocycl. Chem.* **11**, 811 (1974).

⁹⁰ E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.* **6**, 423 (1967).

⁹¹ S. A. Khan, H. Plieninger, D. Wild, and A. Siddiqui, *Chem. Ber.* **106**, 12 (1973).

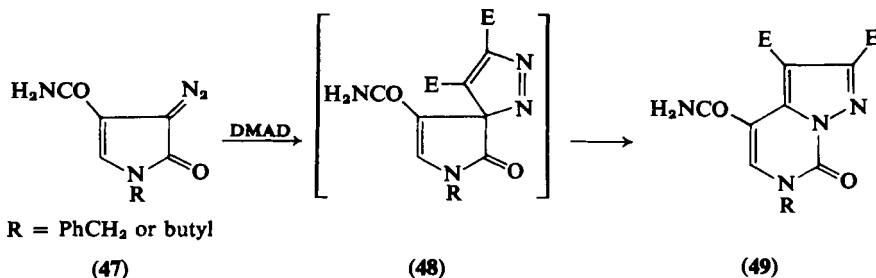


Pyrrolones (45) with DMAD, give pyridines (46)⁹² with loss of carbon monoxide.



3. Dihydropyrroles (Pyrrolines) and Tetrahydropyrroles (Pyrrolidines)

Spiro intermediates (48) have been invoked by Dobeneck and Uhl⁹³ to explain the formation of the pyrazolotetrahydropyrimidines 49 from the diazopyrrolinones 47 and DEAD. A van Alphen rearrangement,⁹⁴ which may be a [1,5] shift, is involved.

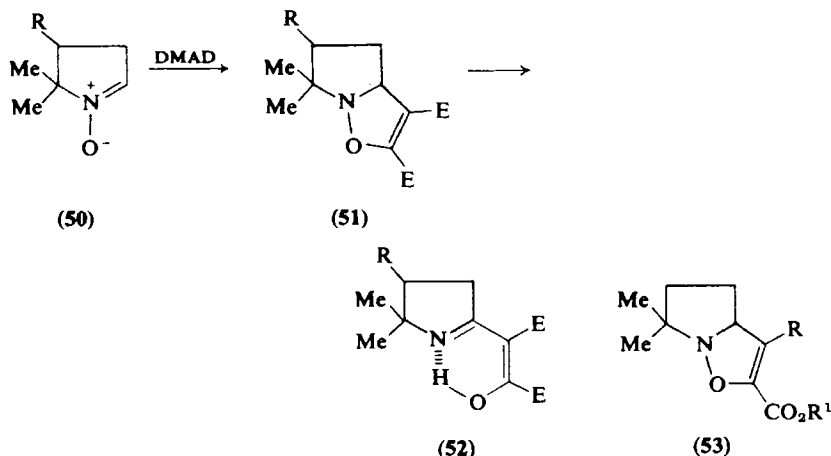


⁹² T. Eicher, F. Abdesaken, G. Franke, and J. L. Weber, *Tetrahedron Lett.*, 3915 (1975).

⁹³ H. von Dobeneck and A. Uhl, *Annalen*, 1550 (1974).

⁹⁴ J. van Alphen, *Rec. Trav. Chim, Pays-Bas* 62, 485 491 (1943).

The Δ^1 -pyrroline-*N*-oxides (**50**) undergo violently exothermic reactions with DMAD in the absence of solvent.⁹⁵ In ether at room temperature, unstable products (**51**) that rearrange exothermically to the pyrrolines (**52**) are formed; this ring fission recalls that of isoxazolium salts.⁹⁶ With unsymmetrical acetylenes, two modes of cycloaddition are possible. Propiolic acid adds to **50** ($R = H$), giving an unstable solid



whose IR spectrum indicated structure **53** ($R = R^1 = H$). Adduct **53** ($R = Ph$, $R^1 = Me$) from **50** ($R = H$) with MPP was stable at room temperature. The more highly substituted nitrone **54** gave a 1:1 molar adduct (**55**) with DMAD together with small amounts of 1:4 molar adducts. At room temperature, **55** is stable, but on heating to 130° an interesting rearrangement leading to the pyrrole **59** was observed. The rearrangement is visualised as a thermally induced fragmentation promoted by nitrogen that proceeded via the enamine **56**, which rearranged to **60** and gave **59** on cyclodehydration,⁹⁵ but an alternative route (**55** \rightarrow **57** \rightarrow **58** \rightarrow **59**) similar to that followed by the reaction between DMAD and phenanthridine 5-oxide is more probable.^{97,98}

With DMAD, both the pyrrolidine **61**⁹⁹ and protoporphyrin IX dimethyl ester (**63**) behave as dienes and undergo Diels-Alder additions yielding **62** and **64**, respectively.^{100,101}

⁹⁵ R. Grigg, *Chem. Commun.*, 607 (1966).

⁹⁶ R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.* **83**, 1007 (1961).

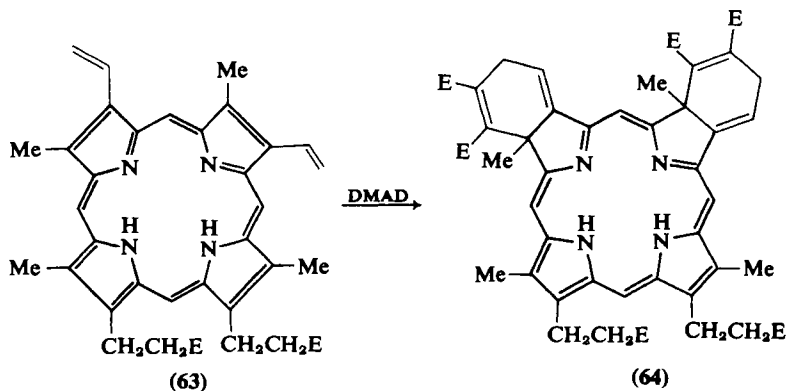
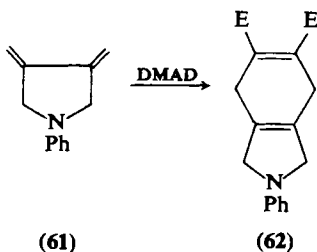
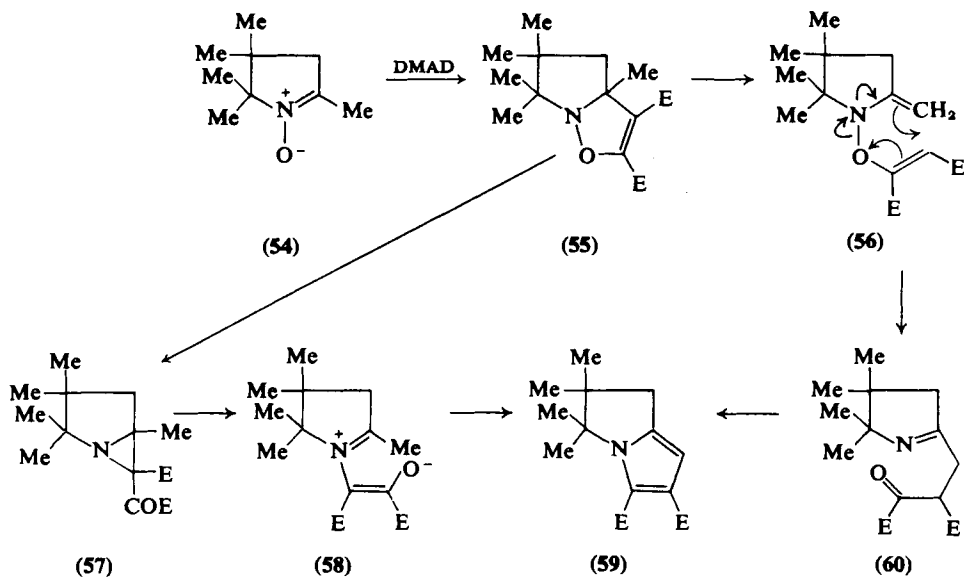
⁹⁷ R. M. Acheson, I. A. Selby, and A. S. Bailey, *Chem. Commun.*, 835 (1966).

⁹⁸ R. M. Acheson, I. A. Selby, and A. S. Bailey, *J. Chem. Soc. C*, 2066 (1967).

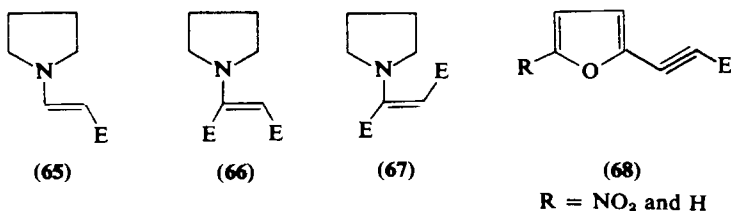
⁹⁹ Y. Gaoni, *Tetrahedron Lett.*, 2361 (1973).

¹⁰⁰ R. Grigg, A. W. Johnson, and A. Sweeney, *Chem. Commun.*, 697 (1968).

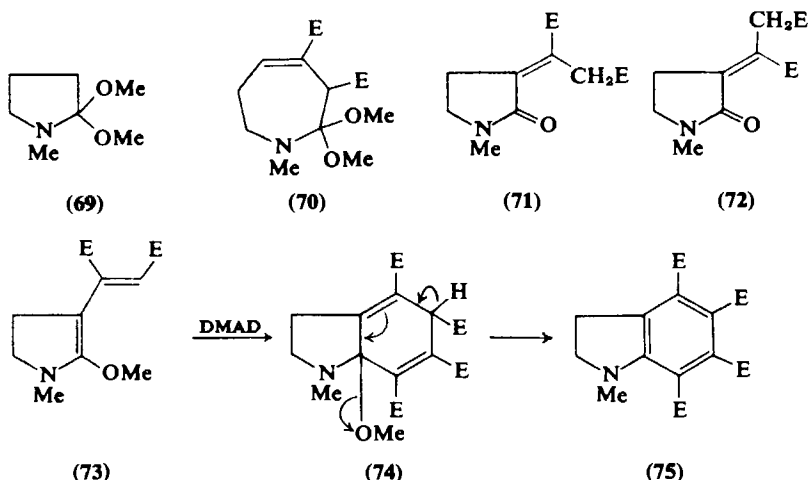
¹⁰¹ H. J. Callott, A. W. Johnson, and A. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1424 (1973).



Russian workers¹⁰² first added pyrrolidine to propiolic, tetrolic, and phenylpropiolic esters. Later,¹⁰³⁻¹⁰⁵ such Michael additions were carried out in various solvents. With MP, pyrrolidine gave the trans adduct **65**, whereas DMAD gave a mixture of maleate (**66**) and fumarate (**67**) esters. Akerblom^{106,107} has described similar additions of pyrrolidine to the furyl (**68**) and phenylpropiolic esters.



Addition of DMAD to 1-methyl-2-pyrrolidine dimethylacetal (**69**) in dioxane¹⁰⁸ gave no **70**, but the indoline **75**, the isomeric pyrrolidones **71** and **72**, and the pyrroline **76** were obtained; using benzene as solvent the 1:1 adduct (**73**) was the major product. With DMAD, compound **73** gave **75**, presumably via **74**.



¹⁰² I. Ya Postovskii, E. I. Grinblat, and L. F. Trefilova, *Zh. Obshch. Khim.* **31**, 400 (1961) [*CA* **55**, 23,541 (1961)].

¹⁰³ E. Winterfeldt and H. Preuss, *Chem. Ber.* **99**, 450 (1966).

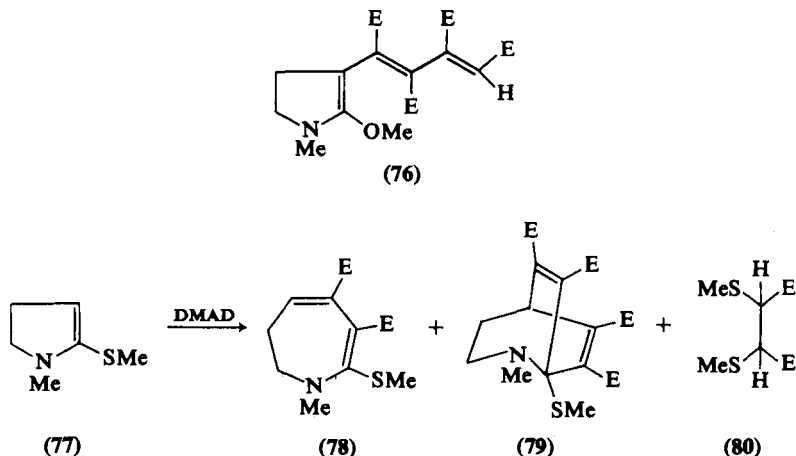
¹⁰⁴ R. Huisgen, K. Herbig, A. Sigel, and H. Hüber, *Chem. Ber.* **99**, 2526 (1966).

¹⁰⁵ K. Herbig, R. Huisgen, and H. Hüber, *Chem. Ber.* **99**, 2546 (1966).

¹⁰⁶ E. Akerblom and A. Norrman, *Chem. Scr.* **2**, 183 (1972) [*CA* **78**, 71,789 (1973)].

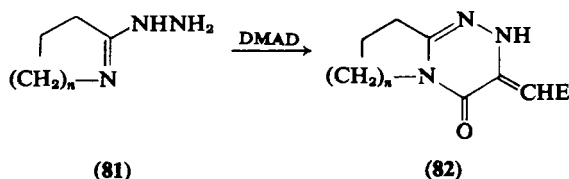
¹⁰⁷ E. Akerblom, *Chem. Scr.* **3**, 232 (1973) [*CA* **79**, 52,690 (1973)].

¹⁰⁸ T. Oishi, S. Murayami, and Y. Ban, *Chem. Pharm. Bull.* **20**, 1740 (1972).

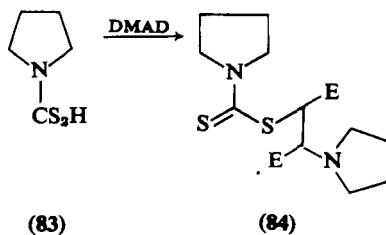


By contrast, 1-methyl-2-methylthio-pyrroline (77) with DMAD in dioxane gave the azepine 78 as major product, along with some of its Diels-Alder adducts 79 (also obtained from 78 and DMAD), 71, 75, and 80; no 72 could be detected.¹⁰⁸

Cyclic amidrazones (81, $n = 1-4$) and DMAD give 1,2,4-triazin-5-ones (82).¹⁰⁹



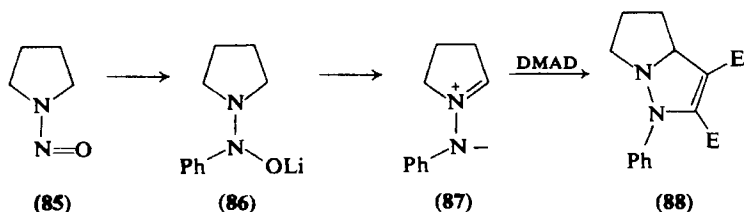
The reaction between pyrrolidine and carbon disulfide readily gives the dithiocarbamate 83; this compound with DMAD gave 84.¹¹⁰



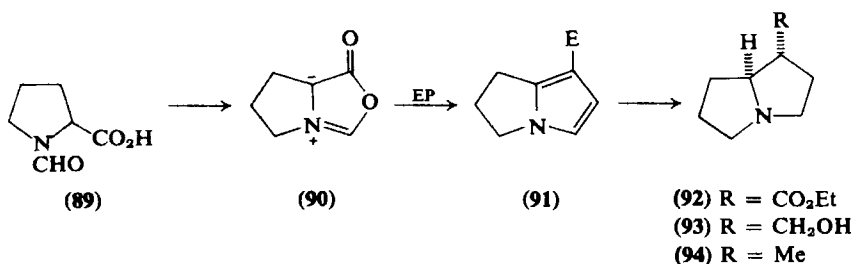
¹⁰⁹ M. Brügger, H. Wamhoff and F. Korte, *Annalen* **757**, 100 (1972).

¹¹⁰ C. S. Angadiyavar and M. N. Gudi, *Indian J. Chem.* **10**, 888 (1972); [*CA* **78**, 71,823 (1973)].

N-Nitrosopyrrolidine (**85**) with phenyllithium gives **86**, which with DMAD forms the pyrrolo[1,2-*b*]pyrazole (**88**), possibly through the dipolar intermediate **87**.¹¹¹



A simple stereospecific synthesis of 1-substituted pyrrolizidines¹¹² starts by heating *N*-formyl-L-proline (**89**) with EP and excess acetic anhydride to give 90% of the pyrrole **91** possibly via the 1,3-dipole **90**. Catalytic reduction of **91** gave **92**, which was converted into **93** and **94**.



Succinimide and DMAD give a Michael 1:1 adduct,¹¹³ but *N*-bromo-succinimide with acetylenic esters in acetic acid led to electrophilic addition of bromine to the triple bond.¹¹⁴

The addition of an acetylenic ester to the anion derived from the pyrrolidine-2,4-dione **96** has been used by Lowe, Ridley, and Yeung^{115,116} in an elegant synthesis of β -lactams related to the cephalosporins. Dibenzyl acetylenedicarboxylate gave a mixture of the fumarate (major product) and maleate (**97**), which could be separated by chromatography. Photolysis of the mixture in the presence of *t*-butylcarbazate gave the lactam **98**, which was isolated only as the *E*-isomer.

¹¹¹ P. R. Farina and H. Tieckelmann, *Tetrahedron Lett.*, 4971, (1970); *J. Org. Chem.* **38**, 4259 (1973).

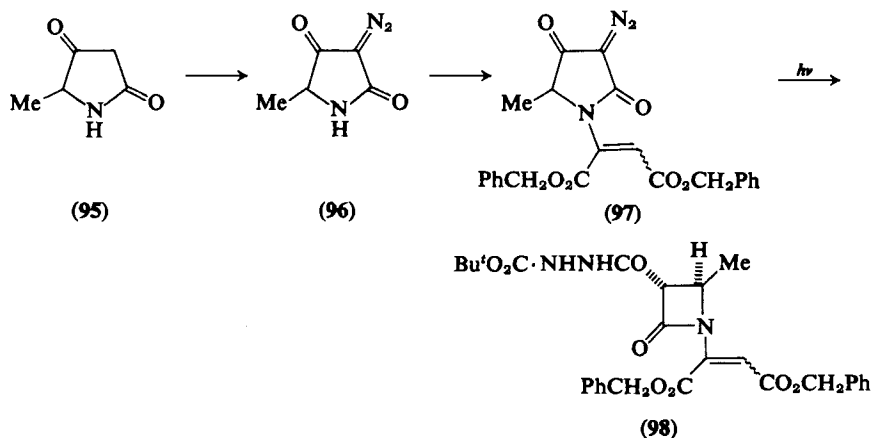
¹¹² M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.* **39**, 731 (1974).

¹¹³ M. N. Gudi and M. V. George, *Indian J. Chem.* **10**, 881 (1972) [*CA* **78**, 147,507 (1973)].

¹¹⁴ A. Iovchev and S. L. Spasov, *Montash*, **100**, 328 (1969) [*CA* **70**, 95,941 (1969)].

¹¹⁵ G. Lowe and D. D. Ridley, *J. Chem. Soc., Perkin Trans. 1*, 2024 (1973).

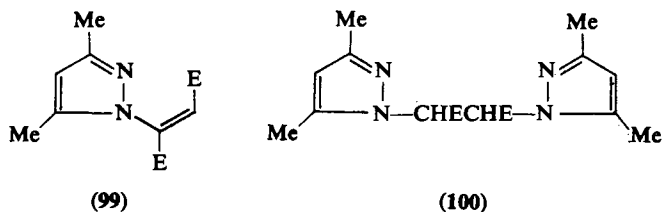
¹¹⁶ G. Lowe and H. W. Yeung, *J. Chem. Soc., Perkin Trans. 1*, 2907 (1973).



B. PYRAZOLES

1. Pyrazole and Alkylpyrazoles

Pyrazole (see also Refs. 117–119) and its 3,5-dimethyl and 3,4,5-trimethyl derivatives combined with half a mole of dimethyl acetylenedicarboxylate give products of similar ultraviolet absorption spectra to the parent pyrazoles. These products (e.g., **100**) do not possess the strong broad absorption at ca. 3310 cm^{-1} characteristic of the bonded N—H group that is present in the parent pyrazoles and are formed by two successive Michael addition reactions. In the case of 3,5-dimethylpyrazole, the initial fumarate (**99**) has been isolated; it showed an absorption spectrum of a more conjugated type than those of the dipyrazolylsuccinates **100**. The addition of MP to pyrazole is mentioned in Section IV,B,2.

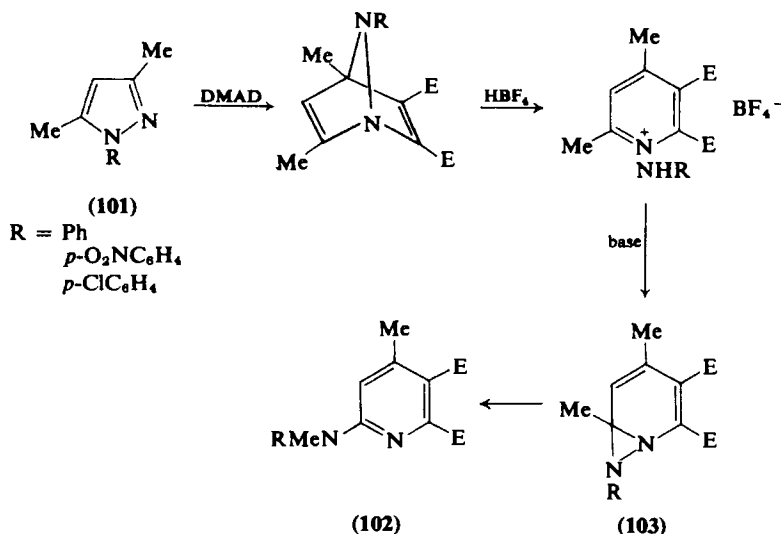


¹¹⁷ H. Reimlinger and J. F. M. Oth, *Chem. Ber.* **97**, 331 (1964).

¹¹⁸ H. Reimlinger and C. H. Moussebois, *Chem. Ber.* **98**, 1805 (1965).

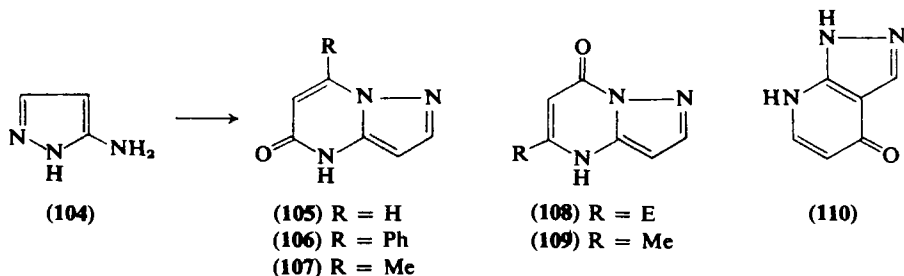
¹¹⁹ R. Huisgen, B. Giese, and H. Hüber, *Tetrahedron Lett.*, 1883 (1967).

Abjean¹²⁰ described the addition of DMAD to various 3,5-dimethylpyrazoles (**101**) in the presence of boron trifluoride; aminopyridines (**102**) are obtained via a methyl migration in **103**, as shown.



2. Aminopyrazoles

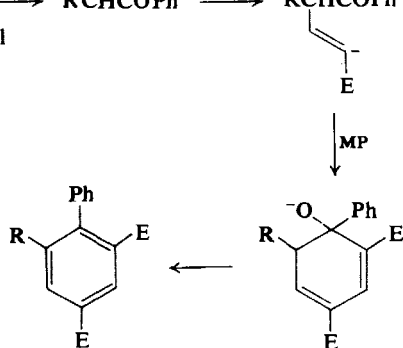
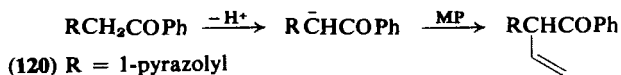
3(5)-Aminopyrazole (**104**) with MP and MPP gave¹²¹ the 5-oxo-4,5-dihydropyrazolo[1,5-*a*]pyrimidines (**105** and **106**), whereas with DMAD the 7-oxo-4,7-dihydro derivative (**108**) was formed. Both types of adduct, **107** and **109**, were obtained from tetrolic ester. In acetic acid, MP and the aminopyrazole gave 4-oxo-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (**110**), a compound which was also formed from **104** and β-ethoxyacrylic ester. The aminopyrazolone **111** gave the isomeric adducts **112** and **113** with DMAD together with a 1:1 molar addition product of DMAD and **112** or **113**.



¹²⁰ F. Abjean, *C. R. Acad. Sci., Ser. C* **278**, 359 (1974).

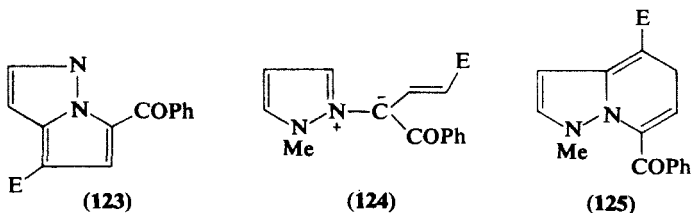
¹²¹ H. Reimlinger, M. A. Peiren, and R. Merényi, *Chem. Ber.* **103**, 3252 (1970).

1-Methyl-2-phenacylpyrazolium iodide with MP in the presence of base also gave an isophthalate (**122**), but in low yield, the pyrazolium ylid **124** being the major product. Attempts to convert the latter into the diazapentalene **125** were unsuccessful.



(121) R = 1-pyrazolyl

(122) R = 2-(1-methylpyrazolium)



5. Pyrazolone Di-N-oxides

Freeman and Hoare¹²⁶ have shown by chemical and spectral methods that heating DMAD with 4*H*-pyrazol-4-one *N,N'*-dioxides (**126**) and monoxides gave 8-oxabicyclo[3,2,1]octane derivatives (**130**) and nitrous oxide, via **127**–**129**. At room temperature the intermediate (**128**) was isolated. With EP and **131** the nitrogen-free, 1:2 adduct **132** was obtained in low yield along with 20% of the pyrimidine **133**.¹²⁷

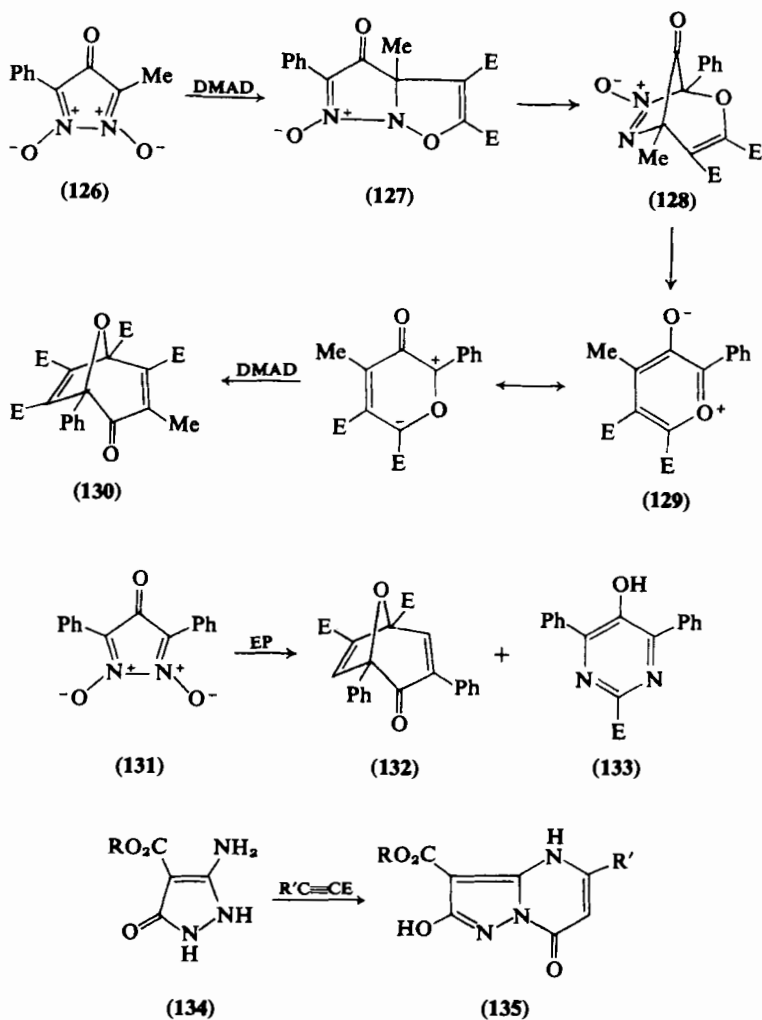
6. Aminopyrazolinones

Acetylenic esters convert aminopyrazolinones (**134**) into pyrazolopyrimidines (**138**).¹²⁸

¹²⁶ J. P. Freeman and M. J. Hoare, *J. Org. Chem.* **36**, 19 (1971).

¹²⁷ J. P. Freeman, E. G. Duthie, M. J. Hoare, and J. F. Hansen, *J. Org. Chem.* **37**, 2756 (1972).

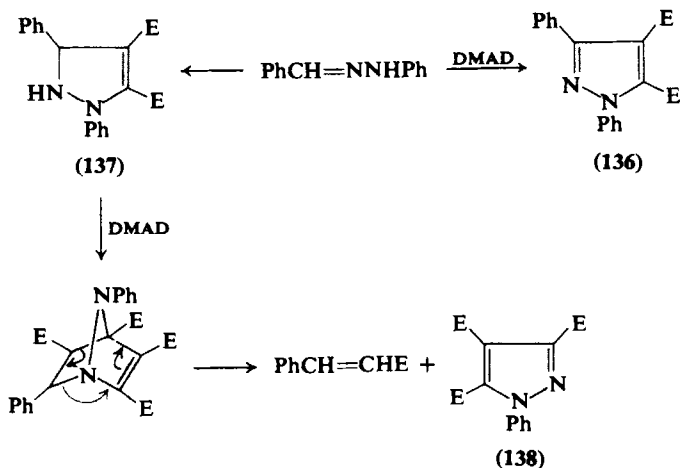
¹²⁸ B. B. Gavrilenko and S. I. Miller, *171st Am. Chem. Soc. Meeting, Mexico City, 1975*, *Abstr.* 161.



7. Pyrazolines

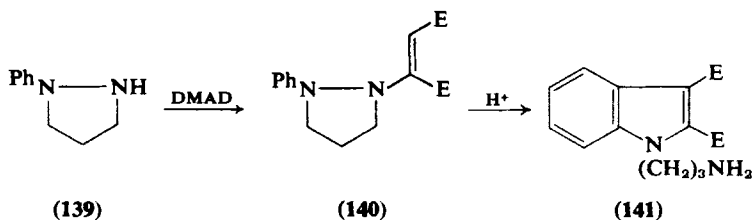
Benzaldehyde phenylhydrazone with DMAD gave 8% of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (136) together with 35% of trimethyl pyrazoletetracarboxylate (138), which the authors suggest is obtained from the primary adduct 137 by Michael addition of a second mole of DMAD followed by cleavage, as shown.¹²⁹

¹²⁹ H. Ogura, K. Kubo, Y. Watanabe, and T. Itoh, *Chem. Pharm. Bull.* **21**, 2021 (1973).



8. Pyrazolidines

Kost and Portov¹³⁰ added DMAD to the pyrazolidine **139** and obtained the Michael adduct **140**, which was, in turn, transformed via a Fischer-type synthesis into the interesting indole **141**.

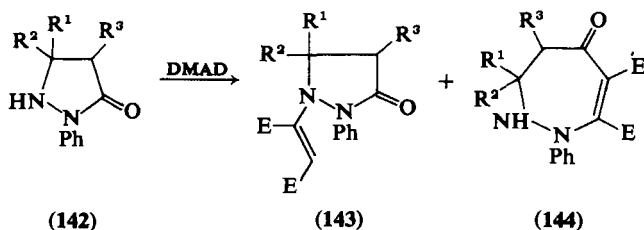


9. Pyrazolidinones

Dimethyl acetylenedicarboxylate with several pyrazolidinones (**142**; $\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}$ or alkyl) gives¹³¹ the normal Michael adducts **143** and the diazepinones **144**; the crystal structure was determined for one diazepinone.

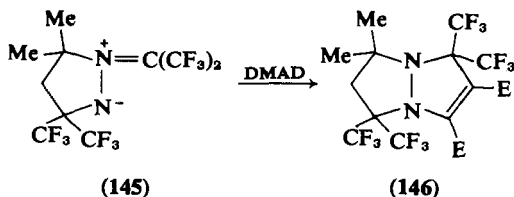
¹³⁰ A. N. Kost and Yu N. Portov, *Khim. Geterotsikl. Soedin.* 371 (1970).

¹³¹ S. N. Ėge, E. Y. Tsui, R. L. Spencer, B. E. Potter, B. K. Eagleson, and H. Z. Friedman, *Chem. Commun.*, 216 (1974).



10. Pyrazolidine Ylids

The azomethine imine **145** from isobutylene and hexafluoroacetone azine, with DMAD, leads to a stable 1:1 adduct (**146**) in 90% yield.^{132,133}



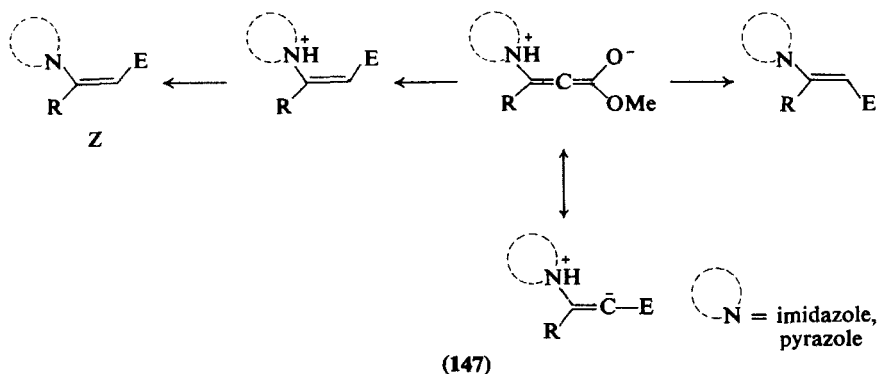
C. IMIDAZOLES

1. Imidazole and Alkylimidazoles

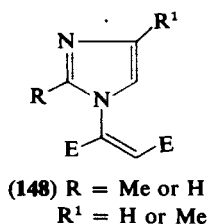
The stereochemistry of the addition of imidazole and pyrazole to MP and DMAD has been examined by Huisgen *et al.*¹¹⁹ Their generalized scheme indicates that both *E* and *Z* adducts arise from the same charged intermediate (**147**), which gives the *E* adduct by internal proton shift and both adducts, but mainly the *Z* adduct, through the agency of external proton donors. The dependence of *E* and *Z* addition on internal and external protonation seems firmly established. The addition of pyrazole to 0.05 molar MP in dioxane and methanol gave 75:25 and 25:75 *E*:*Z* adduct ratios, whereas similar addition to imidazole at 50° gave 35:65 and 19:81 ratios. If the nucleophilic tertiary nitrogen of the imidazole adds to the acetylenic carbon, the NH⁺ group would not be in a position on steric grounds to promote internal protonation.

¹³² K. Burger, W. Thenn, R. Rauh, and H. Schickaneder, *Angew. Chem., Int. Ed. Engl.* **13**, 477 (1974).

¹³³ K. Burger, W. Thenn, R. Rauh, H. Schickaneder, and A. Gieren, *Chem. Ber.* **108**, 1460 (1975).



Although 1-methylimidazole with DMAD gave gums, 2- and 4-methylimidazole gave the fumarates (148).¹³⁴



A different type of adduct (149; R = H) is obtained from 1,2-dimethylimidazole and the ester.⁷² Its structure is supported by oxidation with bromine in methanol to a tetramethyl 2-methylpyridinetetracarboxylate (150)⁷²; the formation of the pyridine tetraester has been confirmed.¹³⁵ When the adduct 149 (R = H) was heated in acetic acid, the indolizine 153 (R = H) was obtained. These results were confirmed¹³⁶; the rearrangement was considered to proceed through ring fission at *a* (149) to give 151 (R = H) followed by loss of methylamine giving 152 and cyclization. The possibility that the supposed 149 is in fact 154, formed by ring opening at *a* and cyclization at the alternative position as in the benzimidazole series, is not excluded by the foregoing data.^{137,138}

¹³⁴ R. M. Acheson, M. W. Foxton, P. J. Abbott, and K. R. Mills, *J. Chem. Soc. C*, 882 (1967).

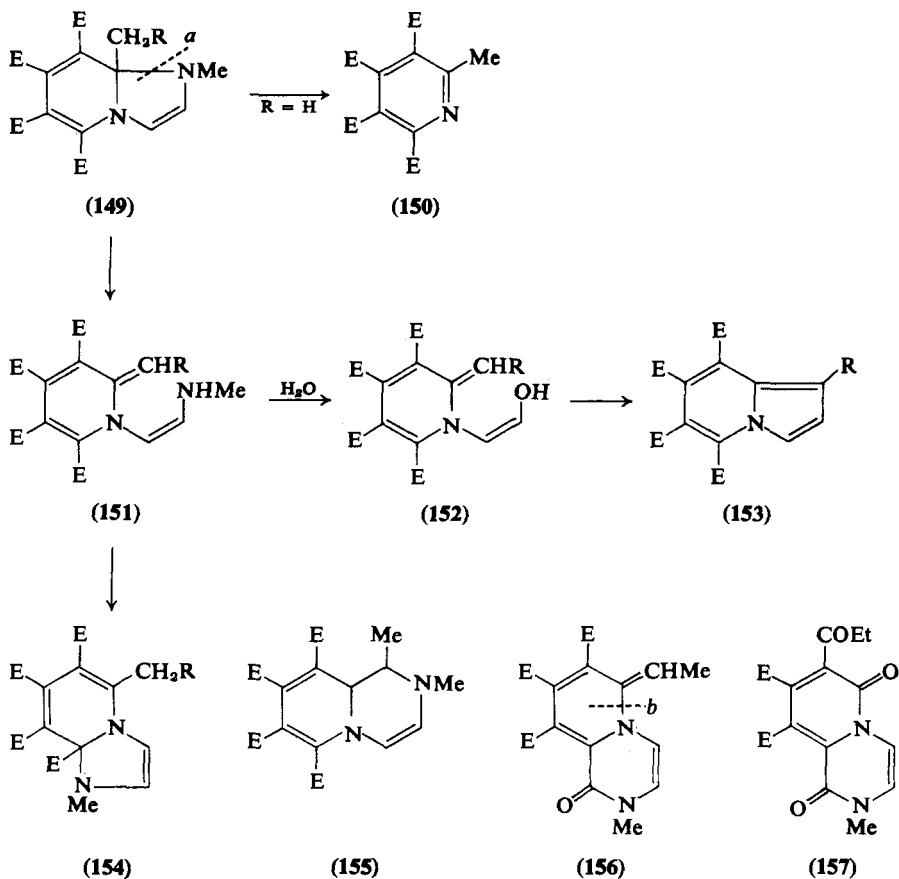
¹³⁵ R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

¹³⁶ R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 4600 (1960).

¹³⁷ P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *Chem. Commun.*, 155 (1975).

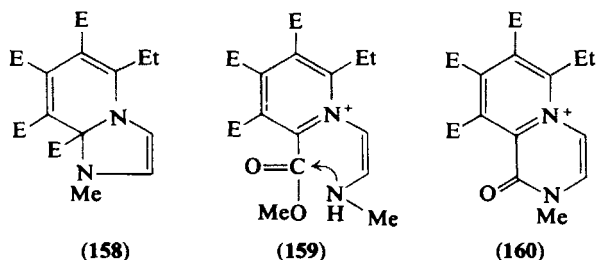
¹³⁸ P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *J. Chem. Soc., Perkin Trans. I*, 1269 (1976).

Crabtree and Johnson¹³⁹ similarly obtained **149** ($R = CH_3$) from 2-ethyl-1-methylimidazole and isolated two products from acetic acid treatment. A red product claimed to be **155** was considered formed via **151** ($R = Me$), followed by an alternative cyclization. The second product, stated to be **156**, was thought to be formed by a cyclization on to the ester group adjacent to the nitrogen atom. It was rather unstable, and rearranged with hot dilute hydrochloric acid to give a compound formulated as **157** and produced from **156** by fission of bond *b*, hydration of the terminal double bond, and condensation of the appropriate ester with the cyclic nitrogen atom.

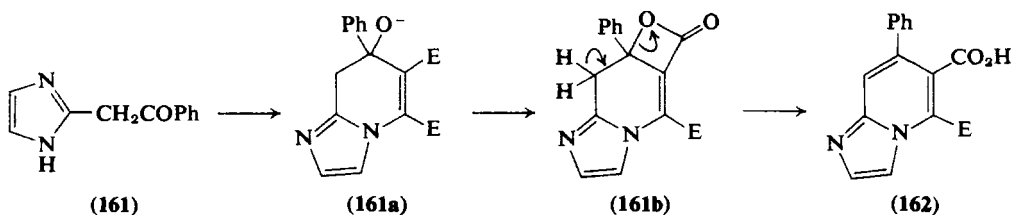


¹³⁹ A. Crabtree and A. W. Johnson, *J. Chem. Soc.*, 1510 (1962).

However, product **155** could well have structure **158**, which is expected to be red, and this on hydrolysis with hydrochloric acid could give **156** and thence **157**, *via* **159** and **160**, as is observed.

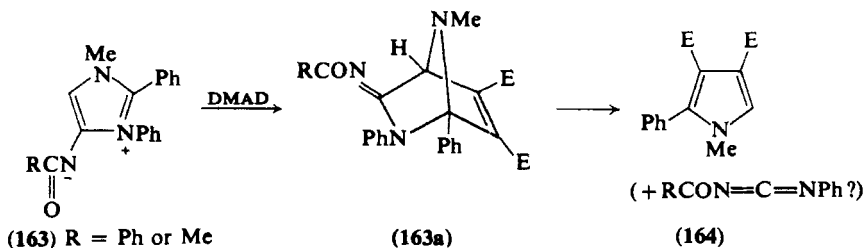


When 2-phenacylimidazole (**161**) was treated with DMAD the imidazopyridine **162** was obtained; using methanol as solvent the yield was 70%, dropping to 40% in acetonitrile. The initial product was formulated as **161a**, which cyclized to **161b** and solvolysis (arrows) now led to the product **162**¹⁴⁰ via a Stobbe-type ring opening.¹⁴¹



2. Compounds from Imidazolium Imines

When **163** was heated with DMAD¹⁴² in benzene, 38–45% of the pyrrole **164** was obtained. A bridged intermediate (**163a**) was postulated,



¹⁴⁰ A. A. Macco, E. F. Godefroi, and J. J. M. Drouen, *J. Org. Chem.* **40**, 252 (1975).

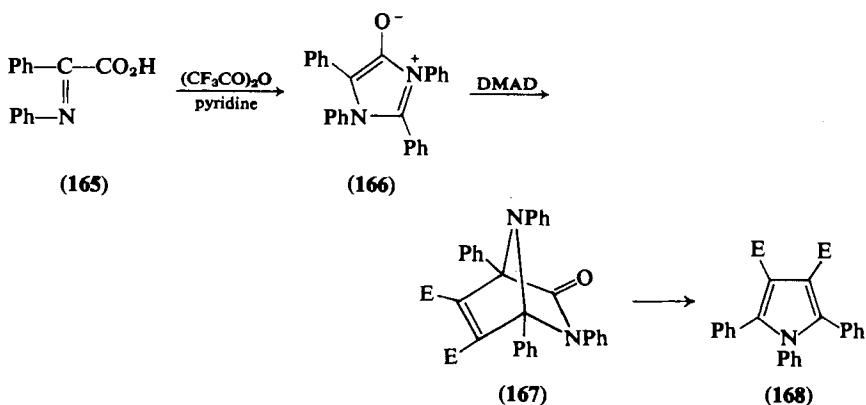
¹⁴¹ W. S. Johnson and G. H. Daub, *Org. Reactions* **6**, 1 (1951).

¹⁴² K. T. Potts and S. Husain, *J. Org. Chem.* **22**, 3368 (1971).

but the other expected product, the *N*-acyl-*N'*-phenylcarbodiimide, was not detected.

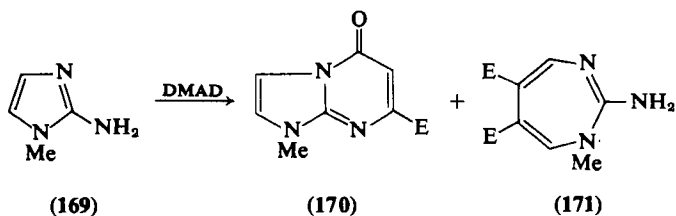
3. Mesoionic Imidazoles

The mesoionic imidazole **166** on refluxing with DMAD in benzene gave the pyrrole **168** almost quantitatively¹⁴³; the postulated intermediate **167** is expected to lose phenyl isocyanate readily. A number of similar reactions involving both EP¹⁴³ and DMAD¹⁴⁴ have been described.



4. Amino and Mercaptoimidazoles

2-Amino-1-methylimidazole (**169**) reacted with DMAD¹⁴⁵ in dioxane to form 30% of imidazo[1,2-*a*]pyrimidone (**170**), identified by the low-field 3-proton, and 5% of the diazepine **171**, which was presumably built up by cyclobutene formation across the 4,5-double bond of **169** and ring expansion.¹⁴⁶ Both 1-methyl-2-methylthioimidazoline and its



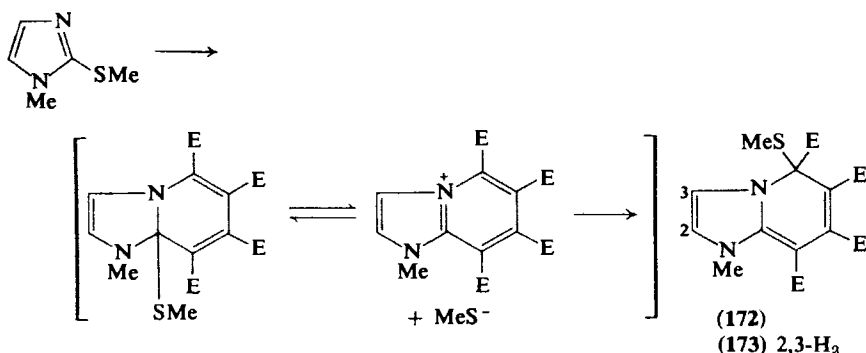
¹⁴³ G. Singh and P. S. Pande, *Tetrahedron Lett.*, 2169 (1974).

¹⁴⁴ M. Hamaguchi and T. Ibata, *Chem. Lett.*, 169 (1975).

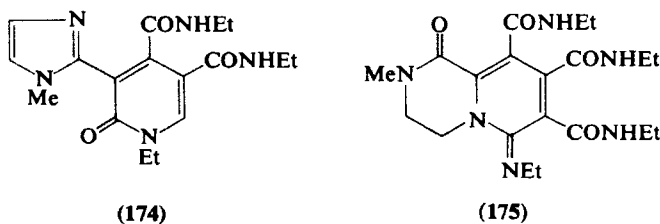
¹⁴⁵ F. Troxler, H.-P. Weber, A. Jaunin, and H. R. Loosli, *Helv. Chim. Acta* **57**, 750 (1974),

¹⁴⁶ H.-P. Weber, T. J. Petcher, A. Jaunin, and F. Troxler, *Helv. Chim. Acta* **58**, 552 (1975).

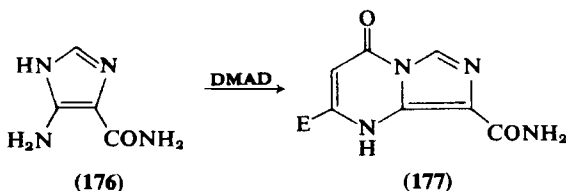
4,5-dihydro derivative with DMAD in acetone give 1:2 molar adducts of the same structural type, which are formed as is shown for **172**. The structures of these compounds arose mainly from desulfurization and



^{13}C NMR spectral studies; whereas **172** with ethylamine gave **174**, the dihydro derivative **173** formed **175**.^{145,146}



5(4)-Aminoimidazole-4(5)-carboxamide hydrochloride (**176**) and DEAD in acetic acid with sodium acetate yielded 41% of imidazo-[1,5-a]pyrimidine-4-one (**177**).¹⁴⁷

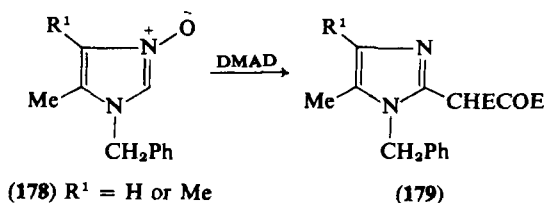


5. Imidazole Oxides

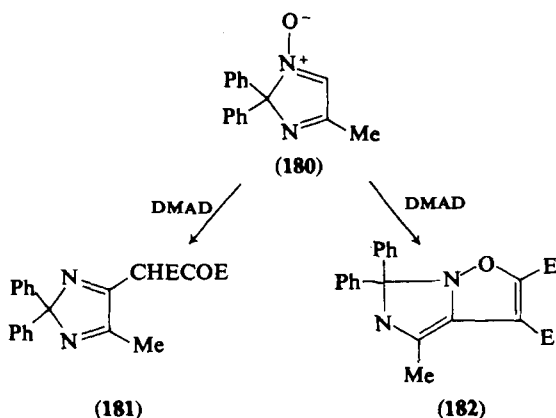
The 1-benzylimidazole-3-oxides **178** with DMAD gave imidazole oxalacetates (**179**) in high yields.¹⁴⁸

¹⁴⁷ T. Novinson, D. E. O'Brien, and R. K. Robins, *J. Heterocycl. Chem.* **11**, 873 (1974).

¹⁴⁸ I. J. Ferguson and K. Schofield, *J. Chem. Soc., Perkin Trans. 1*, 275 (1975).



2,2-Diphenyl-2*H*-imidazole-1-oxide (**180**) cycloadds DMAD: in cold chloroform, the imidazoisoxazole **182** was obtained, whereas in hot benzene the oxalacetate **181** was secured. The type of product is also dependent on the nature of the substituent at the 5-position.¹⁴⁹

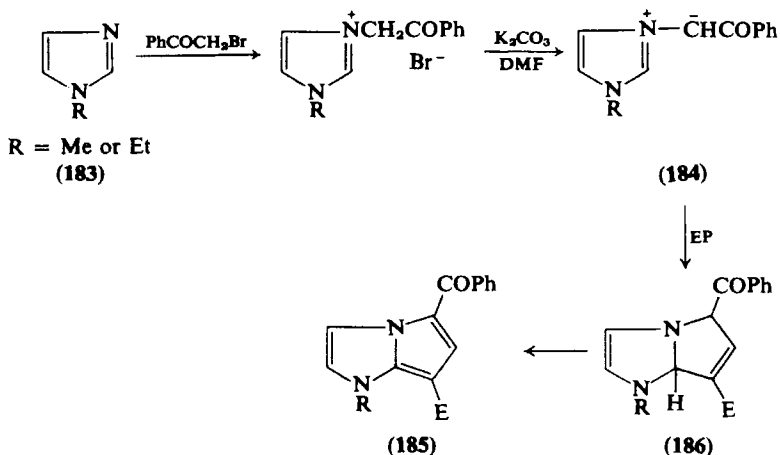


6. Imidazole Ylids

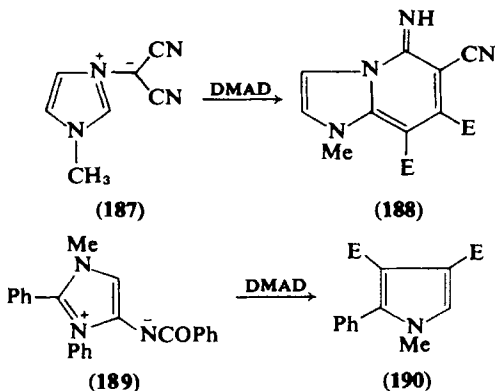
Syntheses of fused heterocycles by 1,3-dipolar cycloaddition reactions to imidazole ylids have been described by several research groups. Boekelheide and Fedoruk¹⁵⁰ quaternized the imidazoles **183** with phenacyl bromide, generated the corresponding ylids **184** and then added excess EP. The anticipated product (**186**) was apparently formed but was dehydrogenated to pyridoimidazole (**185**), which was isolated in 14% overall yield.

¹⁴⁹ B. A. J. Clark, T. J. Evans, and R. G. Simmonds *J. Chem. Soc., Perkin Trans I*, 1803 (1975).

¹⁵⁰ V. Boekelheide and N. A. Fedoruk, *J. Am. Chem. Soc.* **90**, 3830 (1968).



The ylid **187** derived from 1-methylimidazole and bromomalononitrile reacted with DMAD to give imidazopyridine (**188**),¹⁵⁰ whereas imidazolium ylid **189** gave the pyrrole **190**.¹⁵¹



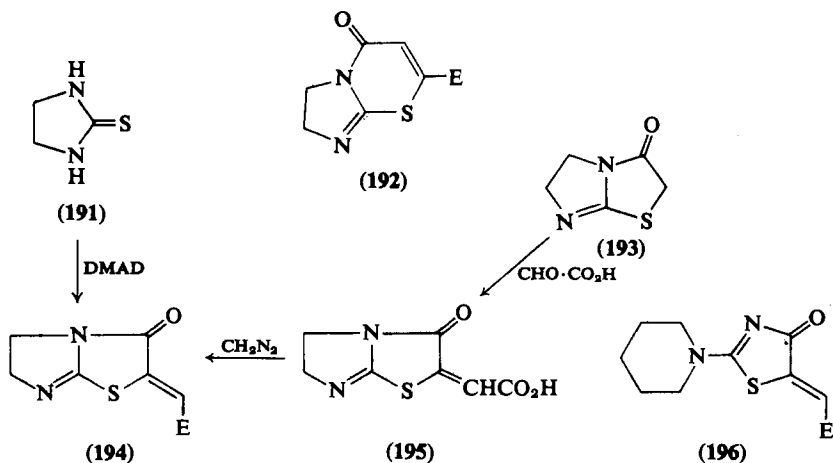
7. Imidazolines

Lown and Ma¹⁵² reacted imidazolidinethione with DMAD and obtained a compound which they described as the imidazothiazine **192**. X-Ray structure analysis¹⁵³ of an analogous compound (**196**) indicated that Lown and Ma's product was, in fact, (**194**), in agreement with the

¹⁵¹ K. T. Potts, S. Husain, and S. Husain, *Chem. Commun.*, 1360 (1970).

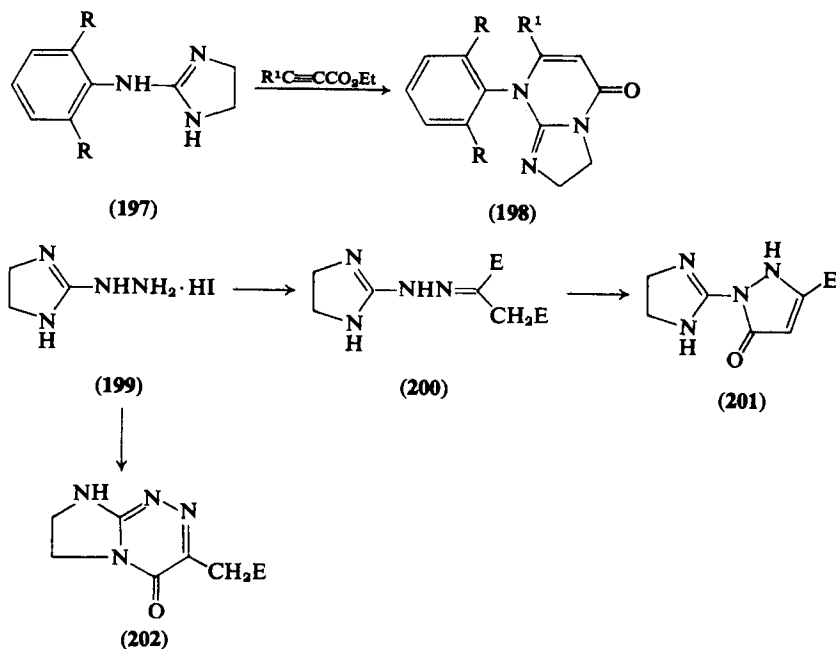
¹⁵² J. W. Lown and J. C. N. Ma, *Can. J. Chem.* **45**, 953 (1967).

¹⁵³ A. F. Cameron, N. J. Hair, N. F. Elmore, and P. J. Taylor, *Chem. Commun.*, 890 (1970); *J. Chem. Soc. B*, 1733 (1971).



synthesis of **194** by Blackshire and Sharpe¹⁵⁴ from the imidazothiazolone **193**.

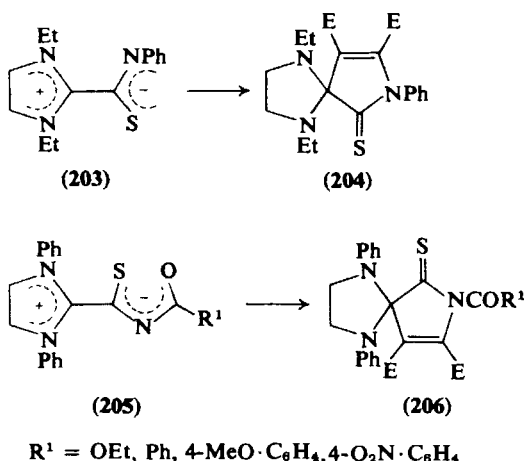
The addition of acetylenic esters to anilinoimidazolines (**197**) gives the imidazopyrimidines **198**.¹⁵⁵ A thorough investigation of the addition



¹⁵⁴ R. B. Blackshire and C. J. Sharpe, *J. Chem. Soc. C*, 3602 (1971).

¹⁵⁵ H. P. Harter, M. Lichti, U. Strauss, and O. Schindler, *Helv. Chim. Acta* **59**, 1203 (1976).

of DMAD to 2-hydrazinoimidazolines (**199**) by Le Count and Greer¹⁵⁶ showed that in methanol a low yield of adduct **200** was obtained and that this was improved by carrying out the addition in aqueous triethylamine. On warming in water, cyclization to **201** took place. Reaction in the presence of triethylamine gave the imidazotriazine **202**.¹⁵⁶



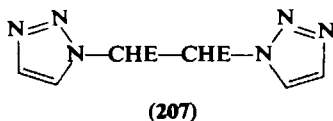
8. Imidazolinium Ions

The imidazolinium zwitterion **203** gave **204** with DMAD,^{157a} and an extension of this work to the derivatives **205** gave the compounds **206**.^{157b}

D. 1,2,3-TRIAZOLES

1. 1,2,3-Triazole with DMAD

1,2,3-Triazole reacts as a secondary amine with DMAD to give the succinate **207**.¹⁵⁸



¹⁵⁶ D. J. Le Count and A. T. Greer, *J. Chem. Soc., Perkin Trans. 1*, 297 (1974).

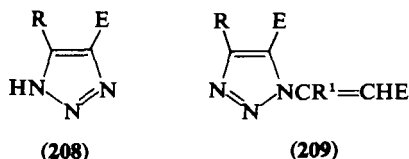
^{157a} H. Behringer and J. Falkenberg, *Tetrahedron Lett.*, 1895 (1967).

^{157b} W. Schoessler and M. Regitz, *Chem. Ber.* **107**, 1931 (1974).

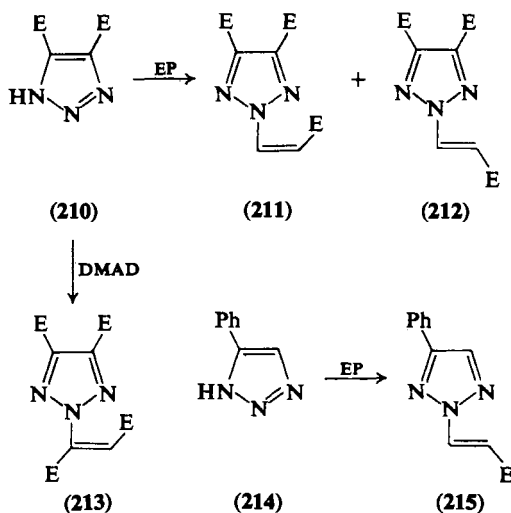
¹⁵⁸ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 389 (1968).

2. 1,2,3-Triazole Esters

Sodium azide in DMSO with ethyl propiolate and DMAD gave the triazoles **208** ($R = H$ and E) together with small quantities of 1:2 adducts that tentatively were assigned structures **209** ($R^1 = H$ and E).¹⁵⁹



The selectivity of the addition of various reagents to 1,2,3-triazoles has been studied by Tanaka and Miller.¹⁶⁰ Treatment of **210** with EP in acetone containing triethylamine gave equal quantities of the adducts **211** and **212**. With DMAD the Michael adduct **213** was obtained. 4-Phenyltriazole (**214**) with EP and sodium methoxide gave **215**, and the authors were unable to find any products derived from attack at N-1 or N-3.



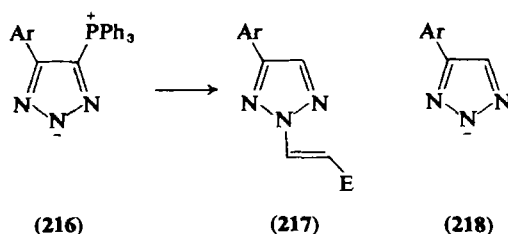
3. 1,2,3-Triazolium Ylids

4-Aryl-5-triphenylphosphonium-1,2,3-triazole ylids (**216**) with MP give high yields¹⁶¹ of adducts **217**, which were also obtainable from the anion **218**.

¹⁵⁹ F. P. Wörner and H. Reimlinger, *Chem. Ber.* **103**, 1908 (1970).

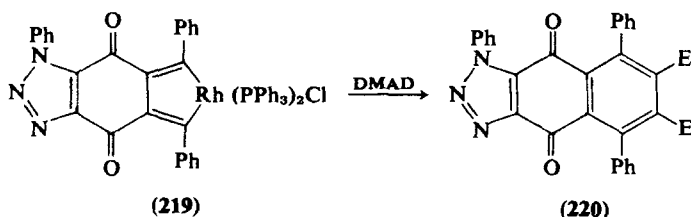
¹⁶⁰ Y. Tanaka and S. I. Miller, *Tetrahedron* **29**, 3285 (1973).

¹⁶¹ Y. Tanaka and S. I. Miller, *J. Org. Chem.* **38**, 2708 (1973).



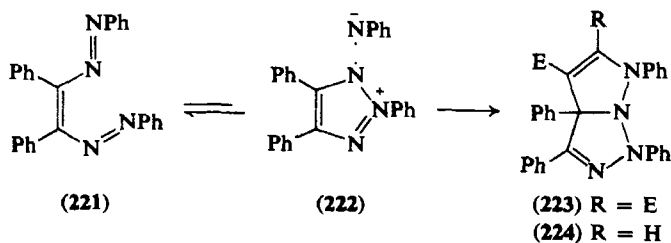
4. Miscellaneous 1,2,3-Triazoles

The rhodium complex **219** gave the naphthoquinone derivative **220** with DMAD¹⁶²; there was no attack at the triazole ring.



5. Mesoionic 1,2,3-Triazoles

Oxidation of benzil diphenylhydrazone is reported¹⁶³ to give **221**, but it has also been suggested¹⁶⁴ that the product is better represented by **222**. This substance with DMAD and MP in acetone gives high yields of 1:1 molar adducts, which have been written¹⁶³ as **223** or **224**.



¹⁶³ E. Muller and W. Winter, *Annalen*, 1876 (1974).

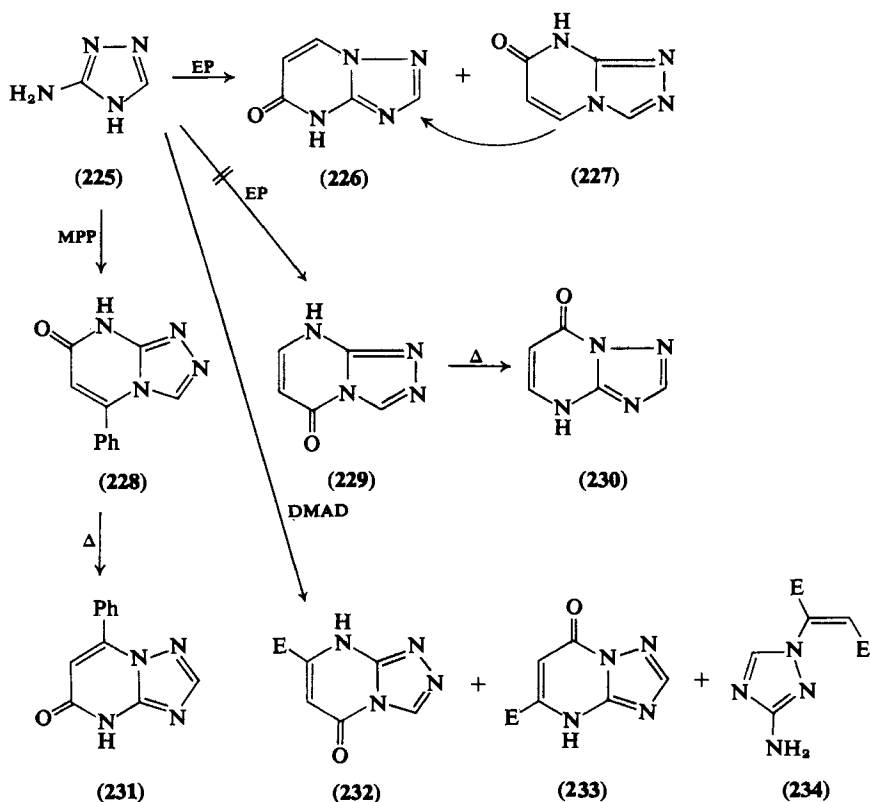
¹⁶³ C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971); *Tetrahedron* **28**, 3987 (1972).

¹⁶⁴ R. B. Woodward and C. Wintner, *Tetrahedron Lett.*, 2697 (1969).

E. 1,2,4-TRIAZOLES

1. 1,2,4-Triazole and Its Amino Derivatives

1,2,4-Triazole behaves like 1,2,3-triazole toward DMAD (cf. 207) in acetonitrile.¹⁵⁸ Reimlinger and Peiren^{165,166} added MP to 3-amino-1,2,4-triazole (**225**) and obtained the triazolo[4,3-*a*]pyrimidine **226** as major product along with an isomer (**227**). Other possible isomeric products, **229** and **230**, were not formed, but were obtained by a different route. Heating **227** with base gave **226**; the latter, together with **230**, which could be obtained by heating **229**, are stable members of this group. 7-Oxo-5-phenyl-7,8-dihydro-*s*-triazolo[4,3-*a*]pyrimidine (**228**) was prepared from MPP and the triazole **225**; thermal isomerization of **228** gave **231**. Addition of DMAD to the triazole **225** gave isomers



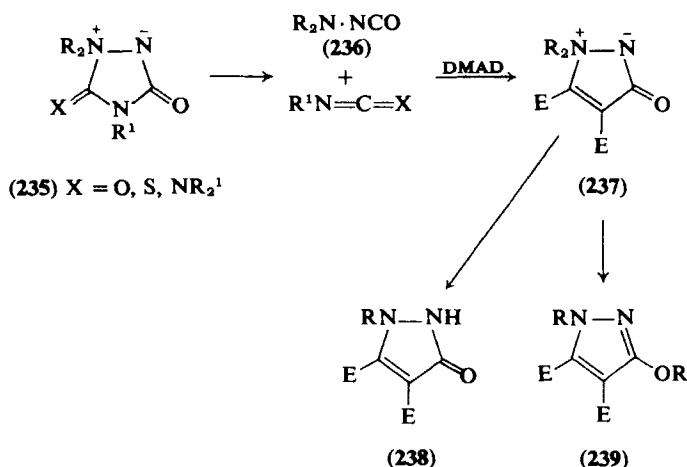
¹⁶⁵ H. Reimlinger and M. A. Peiren, *Chem. Ber.* **103**, 3266 (1970).

¹⁶⁶ H. Reimlinger, R. Jacquier, and J. Daunis, *Chem. Ber.* **104**, 2702 (1971).

232 and **233** together with the Michael adduct **234**. The structures were all deduced from the IR spectra.^{165,168}

2. 1,2,4-Triazolium Ylids

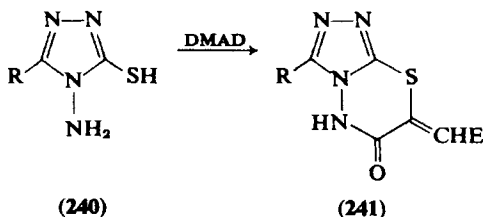
Lockley and Lwowski¹⁶⁷ showed that aminimides (**235**) dissociate upon heating, especially if the substituent at the 4-position is bulky.



The transient *N,N*-dialkylaminoisocyanates (**236**) were trapped with acetylenic esters giving **237**, which were converted by acids into **238**, whereas heating produced an $\text{N} \rightarrow \text{O}$ migration yielding **239**.

3. Mercapto-1,2,4-triazoles

N-Amino-3-mercapto-1,2,4-triazoles (**240**) add DMAD to give adducts **241** derived from initial attack by sulfur.¹⁶⁸

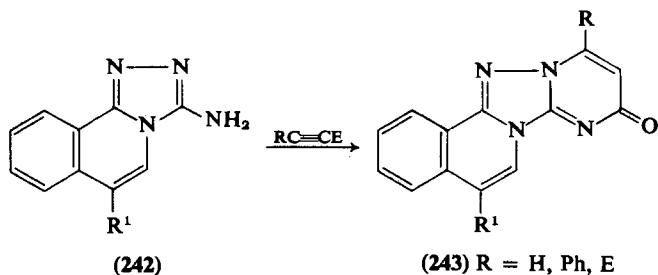


¹⁶⁷ W. J. S. Lockley and W. Lwowski, *Tetrahedron Lett.*, 4263 (1974).

¹⁶⁸ H. Golgolab, *Int. Congr. Heterocycl. Chem.* 4th 1975, p. 351.

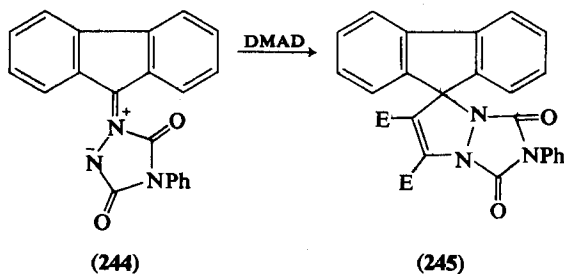
4. Ring-Fused 1,2,4-Triazoles

The 3-amino-1,2,4-triazole **242** with MP, MPP, and DMAD gave¹⁶⁹ the adducts **243**.



5. 1,2,4-Triazolinedione Derivatives

The azomethineimine **244** obtained from *N*-phenyl azodicarboximide and 9-diazofluorene, adds DMAD to give the spiro compound **245**.¹⁷⁰



F. TETRAZOLES

1. Aminotetrazoles

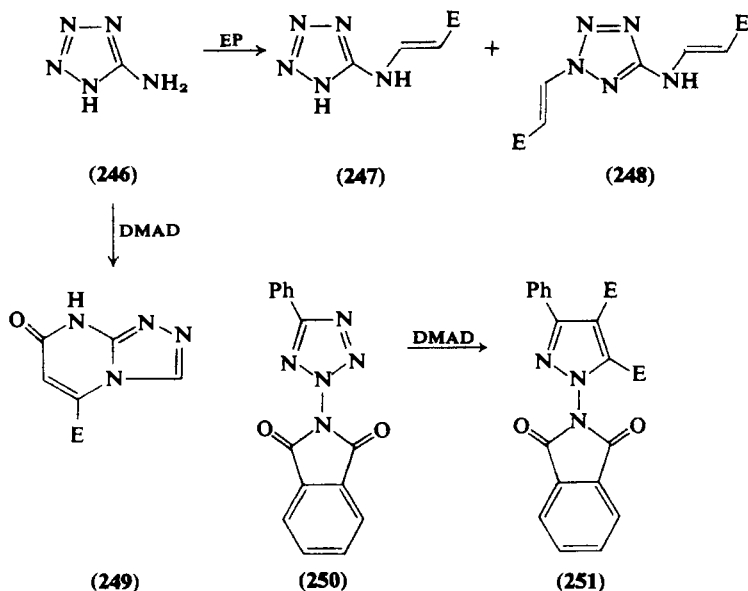
5-Aminotetrazole (**246**) behaves as a secondary amine toward EP giving **247** and **248**, whereas with DMAD it gave **249** and other products.¹⁷¹ Rees and co-workers¹⁷² heated the phthalimidotetrazole **250** with DMAD and obtained a high yield of **251**.

¹⁶⁹ H. Reimlinger, W. R. F. Lingier, J. J. M. Van deWalle, and R. Merényi, *Chem. Ber.* **104**, 3947 (1971).

¹⁷⁰ W. Reid and S-H. Lim, *Annalen*, 1411 (1973).

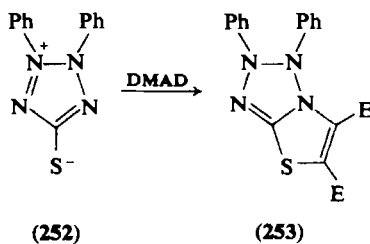
¹⁷¹ H. Reimlinger, M. A. Peiren, and R. Merényi, *Chem. Ber.* **105**, 103 (1972).

¹⁷² T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *Chem. Commun.*, 819 (1973); *J. Chem. Soc., Perkin Trans. 1*, 1747 (1975).



2. Mesoionic Tetrazoles

Dehydrodithizone (252) adds directly to DMAD to give the thiazolo-tetrazole 253 with no loss of fragments that are usually extruded during cycloadditions to mesoionic compounds.¹²⁴

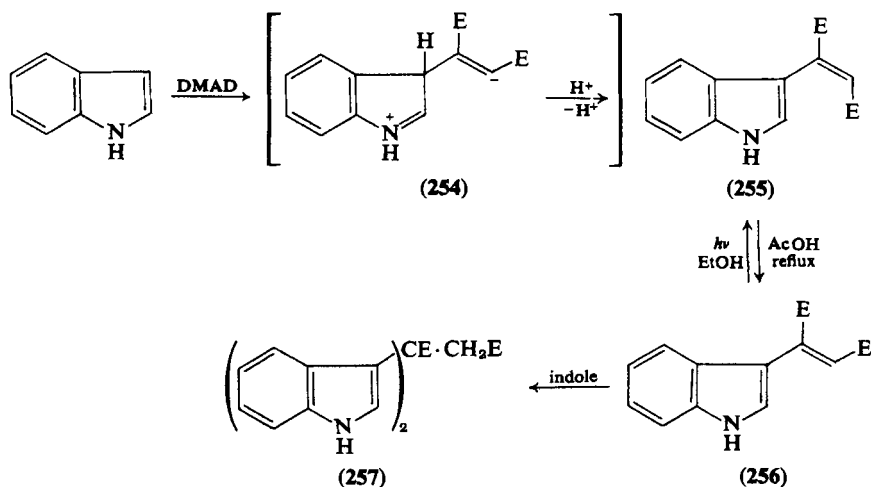


G. INDOLES

1. Indole and Alkylindoles with DMAD

The products obtainable from indole and DMAD depend greatly on the conditions and have been investigated in detail by Acheson *et*

*al.*¹⁷³⁻¹⁷⁵ who found many more products than previously reported.¹ All the reactions of indoles can be interpreted as starting with initial electrophilic attack to give a zwitterion (e.g., **254**), which then undergoes further reactions depending on the circumstances. In methanol, indole and its 1- and 2-methyl derivatives with DMAD yield the corresponding fumarates, e.g., **255**, which are converted to the maleates, e.g., **256** in refluxing acetic acid; irradiation of the maleates gives back the fumarates.¹⁷⁶ The maleates with more indole undergo Michael-type additions to give 2,2-bis(3-indolyl)succinates, e.g., **257**.¹⁷⁵ 1,2-Dimethylindole with DMAD alone probably gives the 1,2-dimethyl derivative of **255**, although the compound has been described¹⁷⁷ as the maleate and 1,3-dimethylindole does not react with DMAD under these conditions. The main products from indole and DMAD in acetic acid are **255** and **257**.¹⁷⁵



1-Methylindole with DMAD in acetonitrile, which had been redistilled from phosphorus pentoxide, gave^{173,174} the azepine **261** which is formed by electrophilic attack at the 3-position of the indole to give **258**, cyclization to **259** and opening of the four-membered ring as is well

¹⁷³ R. M. Acheson and J. N. Bridson, *Chem. Commun.*, 1225 (1971); see also F. Fried, J. B. Taylor, and R. Westwood, *Chem. Commun.*, 1226 (1971).

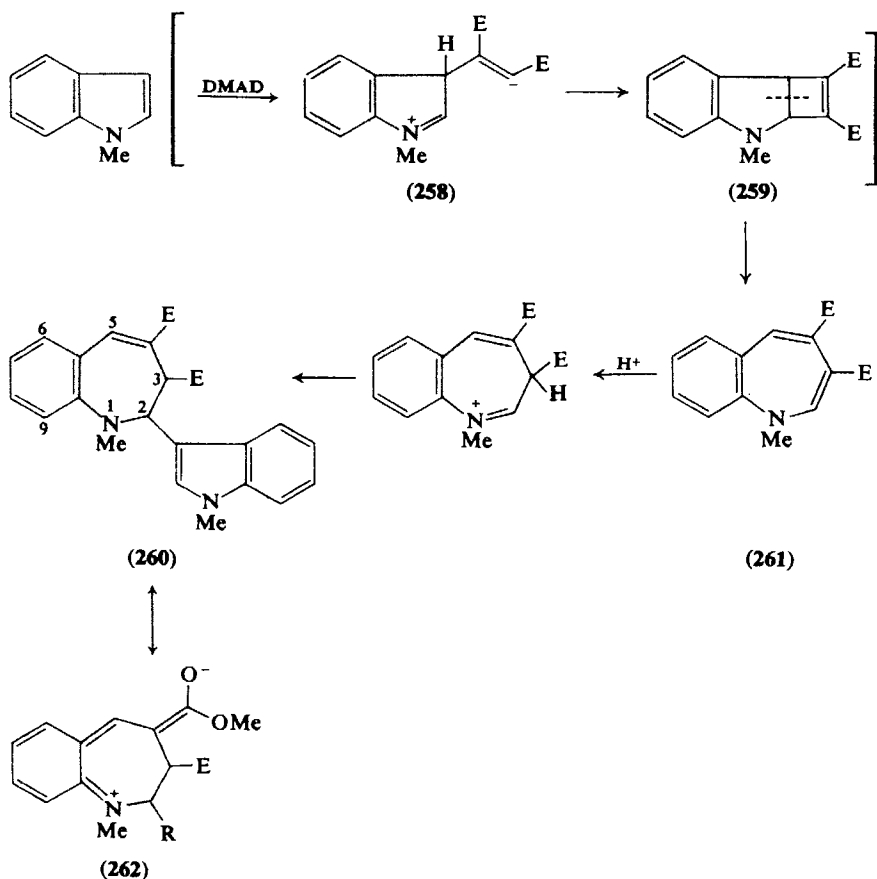
¹⁷⁴ R. M. Acheson, J. N. Bridson, and T. S. Cameron, *J. Chem. Soc., Perkin Trans. 1*, 968 (1972).

¹⁷⁵ R. M. Acheson, J. N. Bridson, T. R. Cecil, and A. R. Hands, *J. Chem. Soc., Perkin Trans. 1*, 1569 (1972).

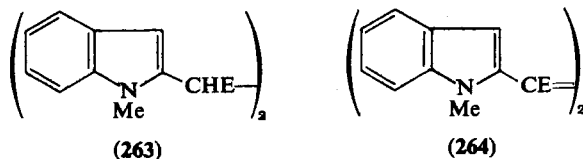
¹⁷⁶ D. C. Johnson, *Diss. Abstr.* **23**, 834 (1962).

¹⁷⁷ R. F. Lange, *Diss. Abstr.* **20**, 1172 (1959).

known for enamines. 3-Amino- and 2-ethoxyindoles (see later) undergo similar reactions, but in the present instance only the heterocyclic nitrogen can provide the electrons needed for the initial attack. Azepine **261** undergoes acid-catalyzed addition of a second mole of 1-methylindole to give the 2-(3-indolyl)azepine (**260**), which is the main product formed from 1-methylindole and DMAD in unpurified acetonitrile. A compound corresponding to **260** is formed from indole and DMAD in purified or unpurified acetonitrile, and a 1:1 adduct analogous to **261** was not detectable.¹⁷⁴ The X-ray crystal structure for

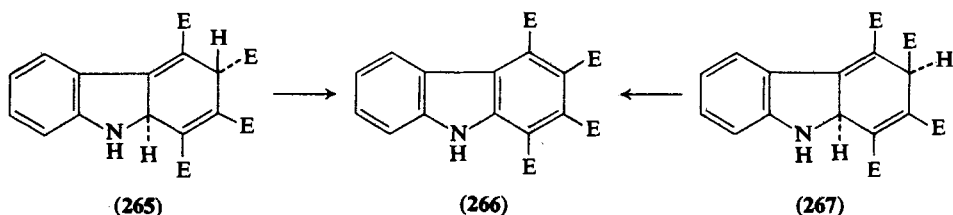


compound **260**, which has been described earlier as having structure **263**⁷² or **264**,¹⁷⁶ is interesting as the azepine nitrogen atom, the 3, 4, 5, 5a, and 9a carbon atoms, and the carbon and oxygen atoms of the 4-ester group, are effectively coplanar with a maximum deviation of

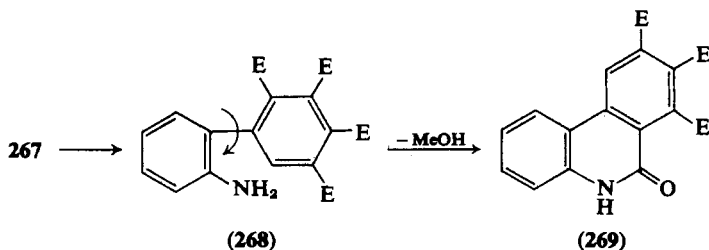


0.072 Å from the best mean plane. This, coupled with the bond lengths, indicates that the resonance structure **262** is important.

Recently¹⁷⁵ fourteen products were separated chromatographically and identified from the reaction of indole with DMAD in the absence of solvent. All were explained as arising from the fumarate **255**, which was isolated, or the maleate **256**; which was not. These compounds could undergo Diels–Alder reactions with DMAD to yield **265** and **267**, respectively, which were not isolated, but on aromatization both would give the carbazole **266**, which was the major product obtained. The main product from the fumarate **255** with DMAD is, in fact, **266**,

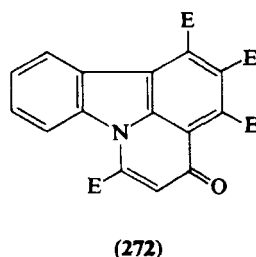
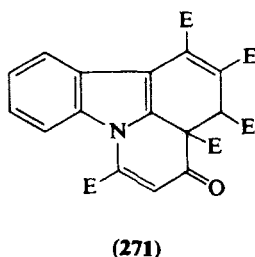
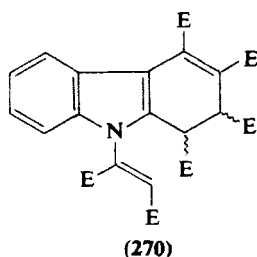


explained by loss of the *trans*-hydrogen atoms of **265** to DMAD as dimethyl fumarate is another reaction product. In the case of **267**, a *trans* elimination of a proton from position 3 and the nitrogen atom from the right-hand ring would lead to aromatization and formation of the aniline **268**, which through loss of methanol would give¹⁷⁵ the phenanthridone **269** actually isolated.¹⁷⁸



¹⁷⁸ R. A. Johnson, *Diss. Abstr.* **26**, 5719 (1966).

Minor products isolated,¹⁷⁵ obtainable by initial Michael additions to **265** and **267**, include the *cis* and *trans* isomers of **270**, **271**, and **272**, and the *N-trans*-1,2-dimethoxycarbonylvinyl derivative of **266**. Four 1:3-



molar adducts of indole and DMAD, possessing N—H absorption in the infrared, were also identified, together with the azepine corresponding to **260**. Complex mixtures were also obtained using benzene as reaction medium. Far fewer crystalline products were isolable when DEAD was reacted with indole.

2. Aminoindoles

Lin and Snieckus¹⁷⁹ heated 1-acetyl-3-piperidinoindole (**273**) with DMAD in dioxane and obtained 98% of the benzazepine **274**, which hydrolyzed to **275** with acid. Benzazepine **277** was prepared with 68% yield from **273** and MP and on this occasion the cyclobutene **276** was isolated.

3. Indole Dithiocarboxylic Acid Derivatives

Tominaga *et al.*¹⁸⁰ studied the cycloaddition of DMAD to 3-indoledithiocarboxylic acid derivatives (**278**). A 2-substituent was essential for success, and **278** ($R^1 = R^2 = R^3 = \text{Me}$) gave a 90% yield of **279**. Similarly, morpholino- and piperidinothioamides **282** formed cycloadducts **283**. Treatment of **279** with methanolic hydrochloric acid gave **281** via the ring-cleaved intermediate **280**.

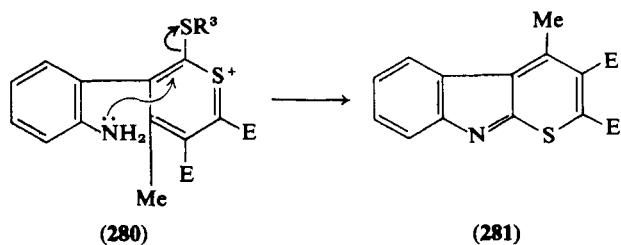
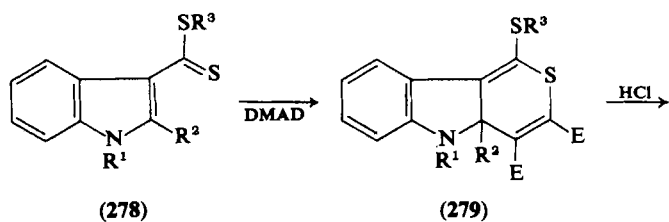
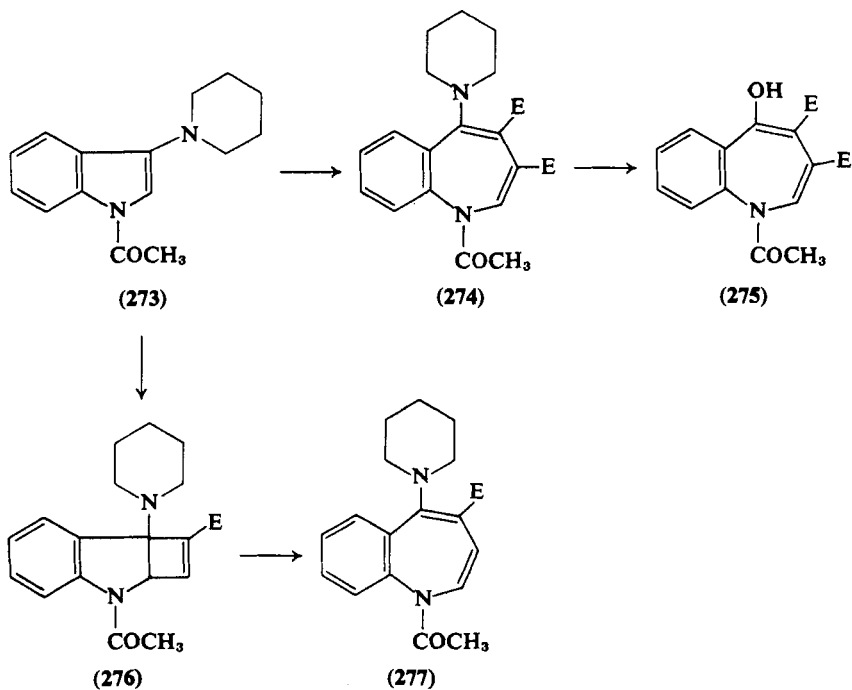
4. Addition of DMAD to Pyrano[2,3-*b*]indoles

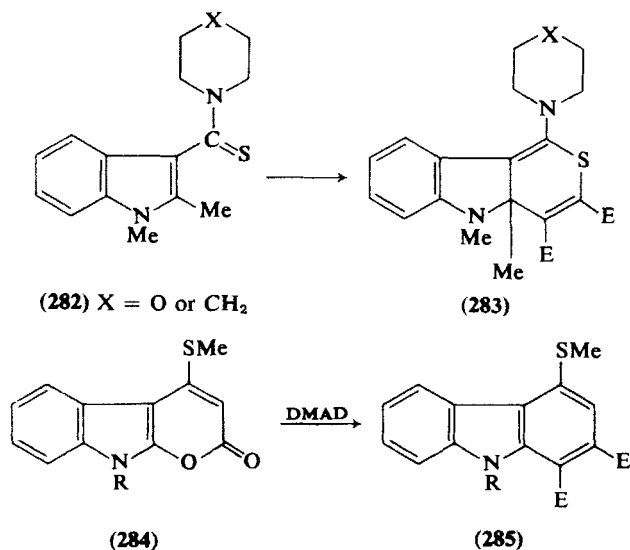
The pyrano[2,3-*b*]indoles **284** reacted with DMAD to give the carbazoles **285**, which have anti-inflammatory activity if $R = \text{H}$ or "lower alkyl."¹⁸¹

¹⁷⁹ M. S. Lin and V. Snieckus, *J. Org. Chem.* **36**, 645 (1971).

¹⁸⁰ Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **21**, 2770 (1973).

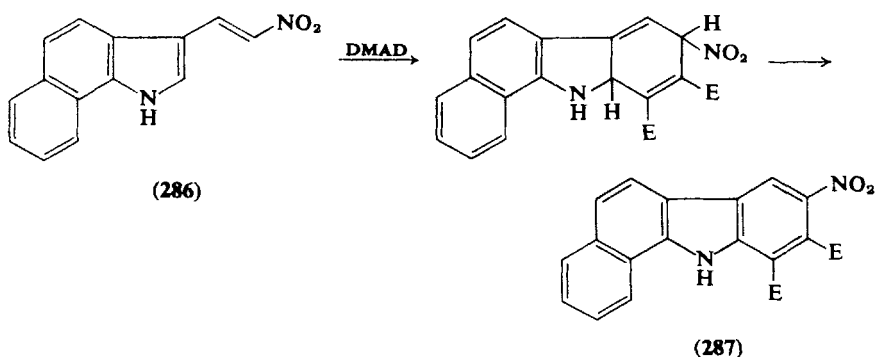
¹⁸¹ G. Kobayashi and Y. Matsuda, Japanese Patent 70 39539 [*CA* **75**, 35,738 (1971)].





5. Nitrovinylindole Derivatives

The nitrovinylbenzindole **286** adds DMAD in a Diels–Alder manner to give the carbazole **287**.¹⁸² This synthesis involves an oxidative step instead of the expected loss of nitrous acid.



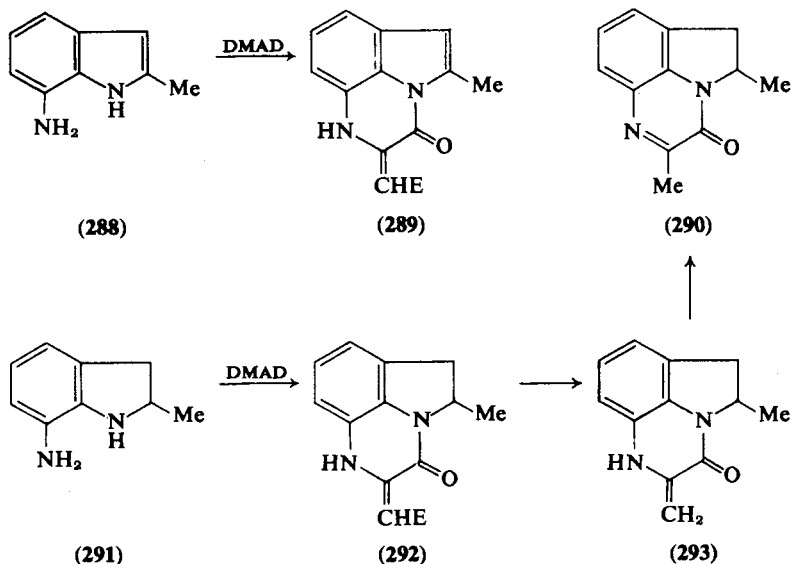
6. 7-Aminoindoles and 7-Aminoindolenines with DMAD

Suschitzky and his collaborators¹⁸³ have synthesized quinoxalinones by the addition of DMAD to the 7-aminoindole **288** and the corre-

¹⁸² S. P. Hiremath, R. S. Hosmane, and S. W. Schneller, *J. Chem. Soc., Perkin Trans. 1*, 2450 (1973).

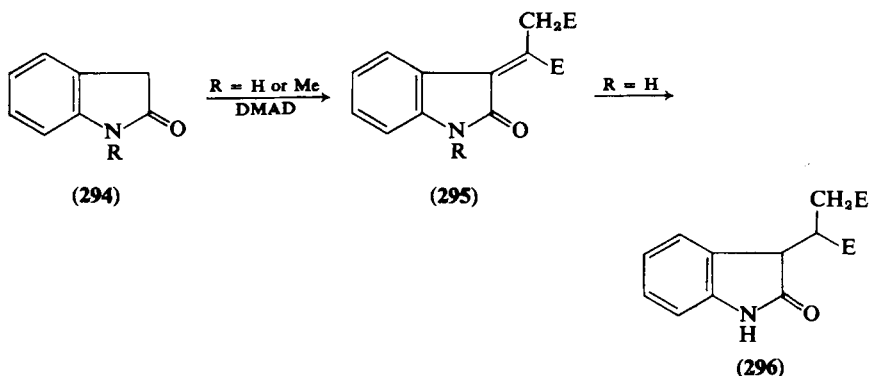
¹⁸³ H. Suschitzky, B. J. Wakefield, and R. A. Whittaker, *J. Chem. Soc., Perkin Trans. 1*, 401 (1975).

spending indolenine **291**. The indole gave **289**, whereas the initial adduct of the indolenine **292** gave the unusual methylene derivative **293** on hydrolysis and decarboxylation. On standing for 3 months, **293** isomerized to **290**.



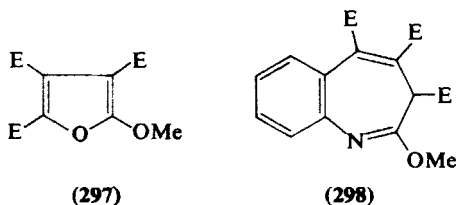
7. Oxindoles

1-Methyloxindole (**294**; R = Me) and DMAD with methanolic sodium methoxide gave two addition products, which from their UV spectra are geometrical isomers of **295** (R = Me), formed by Michael addition and subsequent isomerization.¹⁸⁴

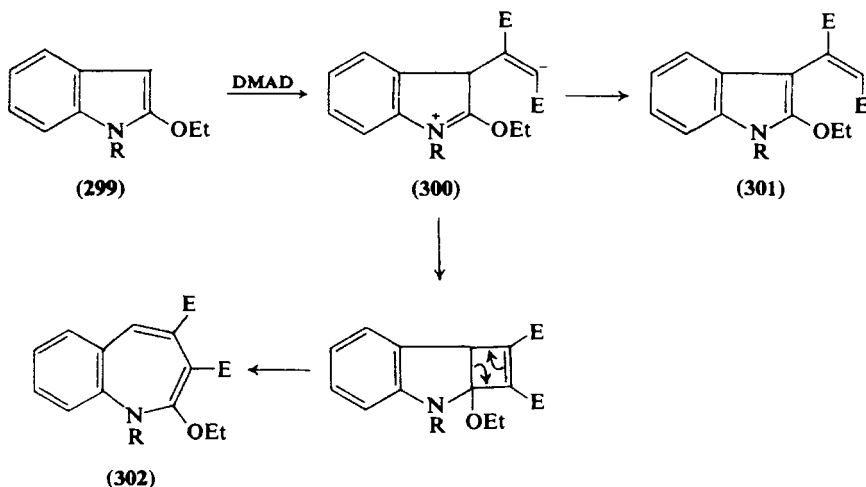


¹⁸⁴ J. A. Ballantine, R. J. S. Beer, and A. Robertson, *J. Chem. Soc.*, 4779 (1958).

Dimethyl acetylenedicarboxylate and the oxindole anion gave **295** ($R = H$), which was hydrogenated to **296**,¹⁸⁵ but oxindole with DMAD at 200° gave the furan **297**,¹⁸⁵ clearly derived by self-condensation of the ester, and the benzazepine **298** the structure and origin of which require further investigation.



The 2-ethoxyindoles **299** ($R = H$ or Me) with DMAD¹⁸⁶ give the Michael adducts **301** and the benzazepines **302**, both via the common intermediate **300**.



Kappeler and Renk¹⁸⁷ heated the 4-ketonaphthostyryl **303** with MP and triethylamine and obtained **304**.

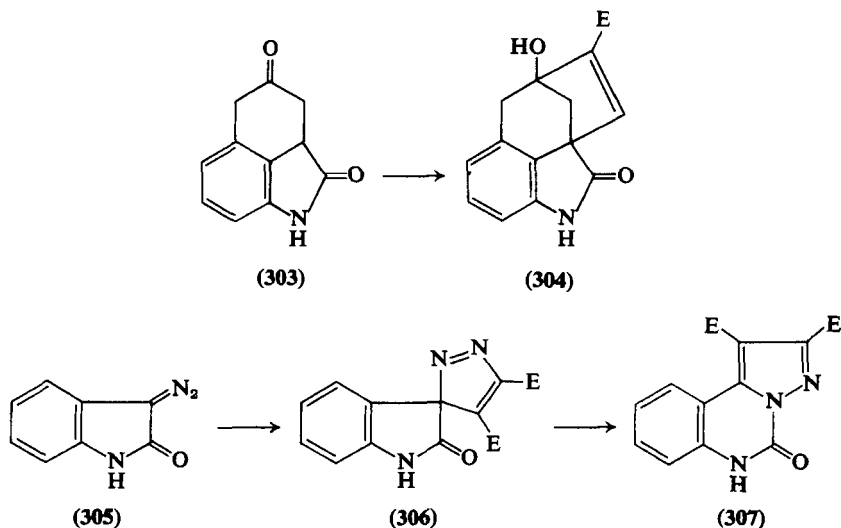
3-Diazoxindole (**305**) adds DMAD to give 83% of the pyrazolo[1,5-*c*]quinazoline (**307**), presumably via **306**.¹⁸⁸

¹⁸⁵ E. Winterfeldt and J. M. Nelke, *Chem. Ber.* **103**, 1183 (1970).

¹⁸⁶ H. Plieninger and D. Wild, *Chem. Ber.* **99**, 3070 (1966).

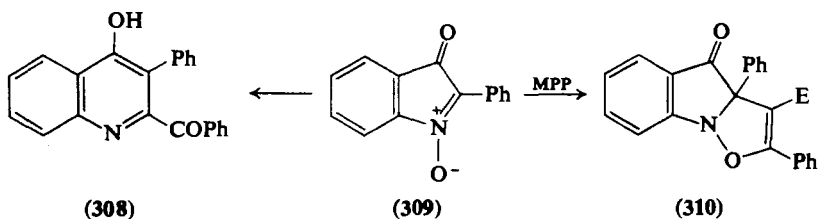
¹⁸⁷ H. Kappeler and E. Renk, *Helv. Chim. Acta* **44**, 1541 (1961).

¹⁸⁸ T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 1417 (1973).



8. Isatogens

Noland and Modler¹⁸⁹ reacted the isatogen **309** with phenylpropionic acid in xylene and obtained 48% of the quinoline **308**. The reaction of **309** with MPP, by contrast, gave **310**.¹⁹⁰



H. ISOINDOLES

1. Polyalkyl-, Polyaryl-, and Polyhaloisindoies

Isoindoles such as 1,3-diphenyl-,¹⁹¹ 1,3,4,7-tetramethyl-, and 2-benzyl-1,3,4,7-tetramethylisoindole¹⁹² react with acetylenic esters across the

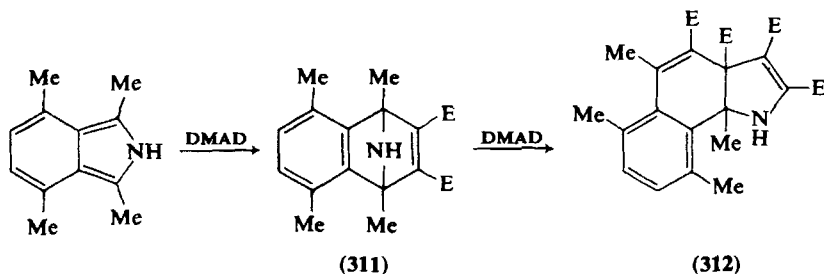
¹⁸⁹ W. E. Noland and R. F. Modler, *J. Am. Chem. Soc.* **86**, 2086 (1964).

¹⁹⁰ H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.* **102**, 904 (1969).

¹⁹¹ J. C. Emmett and W. Lwowski, *Tetrahedron* **22**, 1011 (1966).

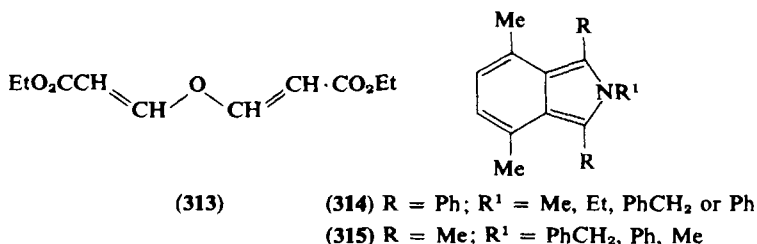
¹⁹² C. O. Bender, R. Bonnett, and R. G. Smith, *J. Chem. Soc. C*, 1251 (1970).

1,3-positions as in the example shown. The 1:1 adduct (**311**) on heating with more DMAD yielded **312**, in a reaction closely similar to that



suggested to account for the product obtained from 1-methylpyrrole and DMAD.⁷¹ Although 2-methylisoindole with DMAD is reported¹⁹³ to give a 2:1 molar adduct, which was not examined further, Kricka and Vernon¹⁹⁴ observed exothermic reactions between DMAD and both 2-ethyl- and 2-*n*-butylisoindoles and obtained products corresponding to **312**; no 1:1 adducts analogous to **311** were detected even when the reactions were performed at 0°.

The reaction between these *N*-alkylisoindoles and EP took a different course¹⁹⁴; the only product isolated was diethyl 3,3'-oxydiacrylate (**313**). Isoindoles **314** and **315** were also prepared and gave 1:1 adducts (cf. **311**) with DMAD, but further addition of the ester was not observed.



The failure of these compounds to form 1:2 adducts was ascribed to steric effects. However, heating the *N*-methyl derivative of **311** split out the nitrogen bridge to give dimethyl 1,4,5,8-tetramethylnaphthalene-2,3-dicarboxylate.¹⁹⁴

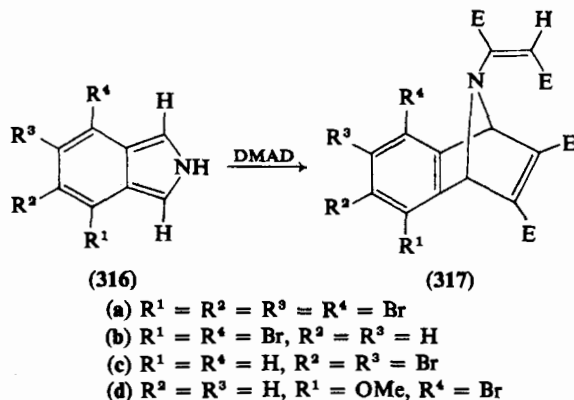
The cyclo and Michael addition of DMAD to the stable di- and tetrabromo-2*H*-isoindoles (**316**) was described by Kreher and Herd.¹⁹⁵

¹⁹³ G. Wittig and H. Ludwick, *Annalen* **589**, 55 (1954).

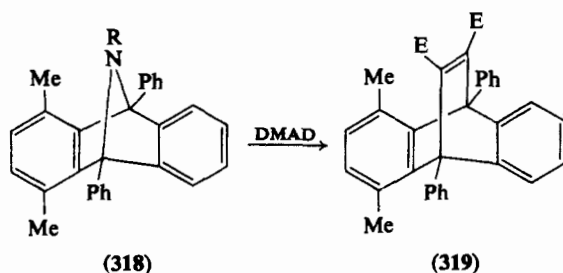
¹⁹⁴ L. J. Kricka and J. M. Vernon, *Chem. Commun.*, 942 (1971); *J. Chem. Soc., Perkin Trans. 1*, 904 (1972).

¹⁹⁵ R. Kreher and K. J. Herd, *Angew. Chem., Int. Ed. Engl.* **13**, 793 (1974).

Compound **316c**, lacking substituents which would sterically interfere with further cycloaddition, underwent this type of reaction leading to a product analogous to **312**. The other compounds in this series by Diels–Alder and Michael additions gave the 1:2 adducts **317**. The



isoindoline **318** on treatment with DMAD gave the bridged anthracene derivative **319** with loss of amine.¹⁹⁶



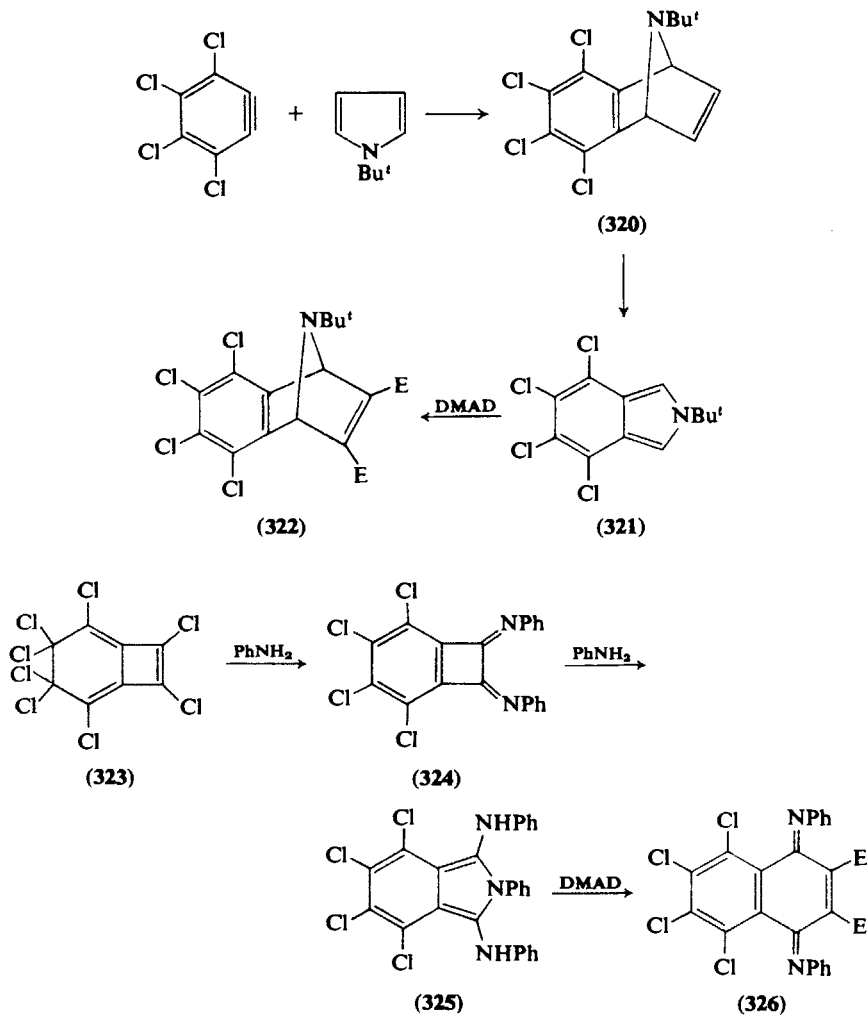
Addition of *N*-*t*-butylpyrrole to tetrachlorobenzynes produced **320**, which, on thermolysis above 200°, gave the isoindole **321**; Diels–Alder addition of DMAD to the latter gave the dihydronaphthalene **322**.¹⁹⁷

Roedig *et al.* described the treatment of polyhalogenated bicyclo-[4,2,0]octa-1,5,7-trienes (**323**) with aniline to give first **324** and then **325**, which with DMAD formed the naphthoquinonebisimine **326**.¹⁹⁸

¹⁹⁶ L. J. Kricka and J. M. Vernon, *J. Chem. Soc., Perkin Trans. I*, 766 (1973).

¹⁹⁷ M. Ahmed and J. M. Vernon, *Chem. Commun.*, 462 (1976).

¹⁹⁸ A. Roedig, G. Bonse, and U. Kuhnel, *Chem. Ber.* **108**, 1156 (1975).



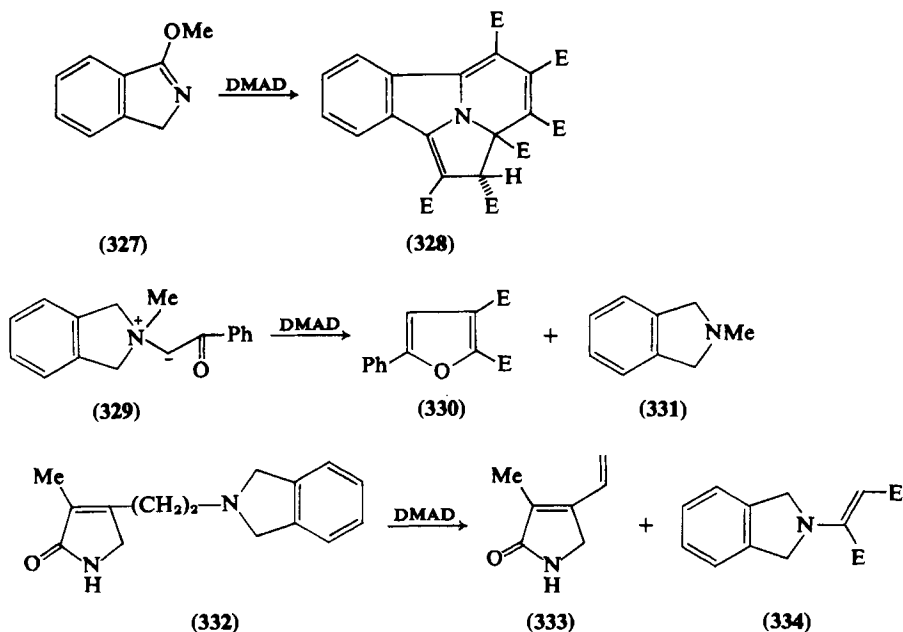
2. 1*H*-Isoindoles and Dihydroisoindoles with DMAD

Treatment of 1-methoxyisoindolenine (327) with 3 moles of DMAD in ether at room temperature gave 38% of dihydroisoindolo[3,2,1-*cd*]-indolizine (328)¹⁹⁹; the structure of this compound has been confirmed by X-ray crystallography.²⁰⁰

¹⁹⁹ K. Kreher and H. Henninge, *Z. Naturforsch. B.* **28**, 801 (1973) [*CA* **81**, 13,341 (1974)].

²⁰⁰ H. J. Lindner and B. von Gross, *Z. Naturforsch. B.* **28**, 545 (1973) [*CA* **81**, 7184 (1974)].

Addition of DMAD to the carbonyl-stabilized nitrogen ylid **329** gave the furan **330** and the isoindolenine **331**. This and similar reactions²⁰¹ could involve either a symmetry allowed concerted cycloaddition or a nonconcerted reaction followed by elimination of the tertiary amine.



The reaction of DMAD with the pyrrolinone **332** has been used²⁰² for the synthesis of vinylpyrrolinones (**333**), which are useful for the preparation of bile pigments; the isoindole **324** was also obtained.

I. INDAZOLES

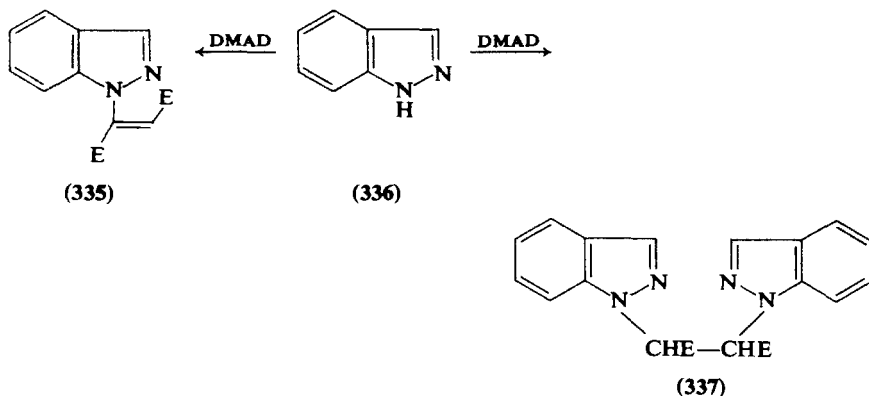
1. Indazole and Arylindazole Derivatives

Benzo[*c*]pyrazoles (**336**) not possessing an N-substituent undergo Michael-type additions to DMAD in ether or acetonitrile to give the dimethyl succinate **337**; sometimes the intermediate fumarate **335** is isolated.²⁰³

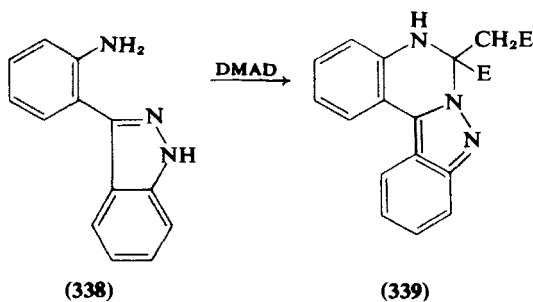
²⁰¹ R. W. Jemison, S. Mageswaran, W. D. Ollis, S. E. Potter, A. J. Pretty, I. O. Sutherland, and Y. Thebtaranonth *Chem. Commun.* 1201 (1970).

²⁰² H. Plieninger, K-H. Hentschel, and R. D. Kohler, *Annalen*, 1522 (1974).

²⁰³ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 389 (1968).

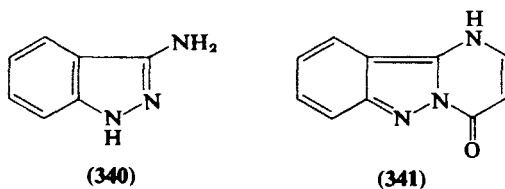


Fryer *et al.*²⁰⁴ obtained **339** from the indazole **338** by addition of DMAD.



2. Amino- and Diazoindazoles

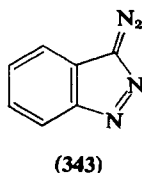
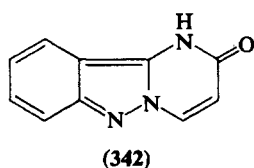
3-Aminoindazole (**340**) with EP gave a compound having either structure **341** or **342**.²⁰⁵ The work of Plescia¹²² with tetrahydrobenzopyrazoles (described in Section IV,B,2) indicates that **342** is correct. 3-Diazo-3*H*-indazole (**343**) with DMAD regenerated indazole.²⁰⁶



²⁰⁴ A. Walser, W. J. Zally, and R. I. Fryer, *J. Heterocycl. Chem.* **11**, 863 (1974).

²⁰⁵ H. Reimlinger, M. A. Peiren, and R. Merényi, *Chem. Ber.* **105**, 794 (1972).

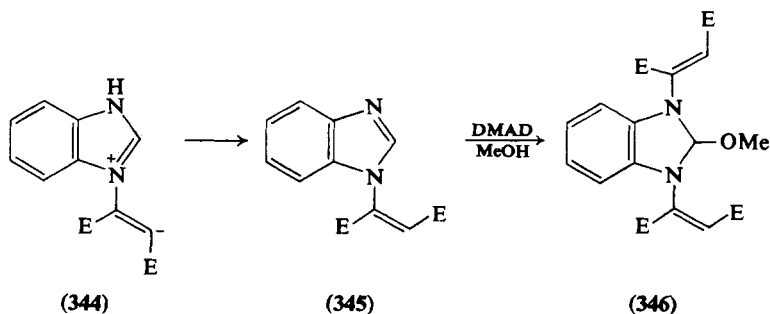
²⁰⁶ D. Fortuna, B. Stanovnik, and M. Tisler, *J. Org. Chem.* **39**, 1833 (1974).



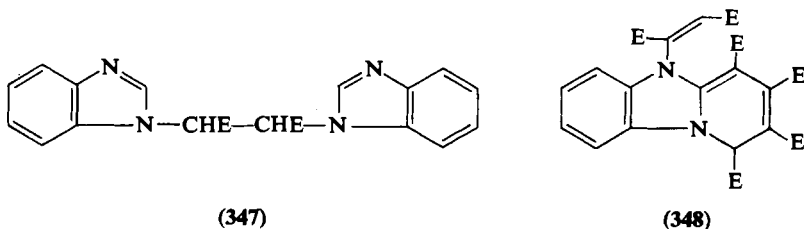
J. BENZIMIDAZOLES

1. *N*-Unsubstituted Benzimidazoles with DMAD

Benzimidazoles with DMAD give various products. In benzene-methanol,¹³⁴ 2 moles of the ester yield mainly **346**, with some of the trans-trans isomer, presumably via **344** and **345**. 2-Benzylbenzimidazole

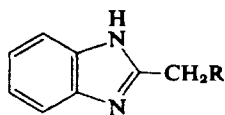


in pure benzene forms the 2-benzyl derivative of **346**.²⁰⁷ Two moles of benzimidazole and 1 mole of DMAD in benzene, however, yield **347**,¹³⁴ comparable to the pyrazole adduct **100**, whereas if excess DMAD is present the product is **348**,¹³⁴ which is presumably formed from **345**, the 3,2-positions behaving like the 1,2-positions of pyridine with DMAD.

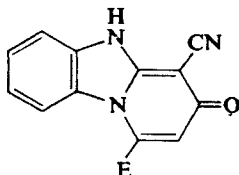


²⁰⁷ R. M. Acheson and W. R. Tully, *J. Chem. Soc. C*, 1623 (1968).

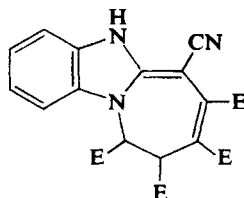
2-Benzimidazolylacetonitrile (**349**) with DMAD in acetonitrile yields a mixture of **351**, **352**, and **353**.²⁰⁸ Nucleophilic attack from the activated methylene group of **349** on an intermediate corresponding to **345** would give **351** and **352** could be formed, as is one product (see **23**, Section X,B) from 2,4-dimethylthiazole. Ethyl 2-benzimidazolylacetate (**350**) also gives a tetracyclic compound (**354**) along with **355**,²⁰⁹ which could be formed via nucleophilic attack starting from the active methylene group. However, the nitrile **349** and the ester **350** in dimethylformamide gave moderate yields of compounds considered²⁰⁹ to be pyridones (e.g. **356**) and which are isomeric with the compounds (e.g., **351**) formed in acetonitrile.



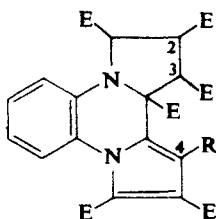
(349) R = CN

(350) R = CO₂Et

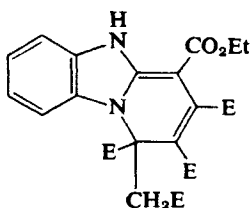
(351)



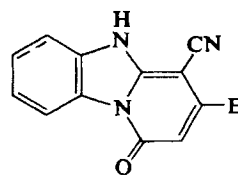
(352)



(353) R = CN

(354) R = CO₂Et

(355)



(356)

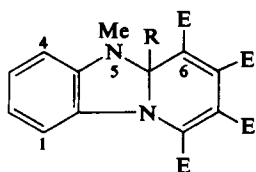
2. *N*-Substituted Benzimidazoles with DMAD

1-Methylbenzimidazole with DMAD in acetonitrile gave¹³⁴ the yellow **360**, readily oxidized by bromine in perchloric acid to a pyrido-[1,2-*a*]benzimidazolium salt, and an isomeric red compound originally thought to have structure **357**, and consequently it was surprising that oxidation did not follow the same course as for **360**. The red compound is best prepared from the reactants in toluene and has now been identi-

²⁰⁸ R. M. Acheson and M. S. Verlander, *J. Chem. Soc., Perkin Trans. 1*, 1577 (1972).

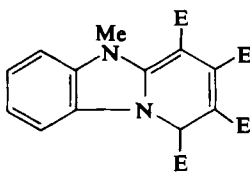
²⁰⁹ N. Finch and C. W. Gemenden, *J. Org. Chem.* **35**, 3114 (1970).

fied¹³⁸ as **361** from its ¹³C NMR spectrum. It could be formed from the possible intermediate **357**, by ring opening and recyclization, as in the thiazole series (cf. **13** → **16**, Section X,B). The same intermediate (**357**)

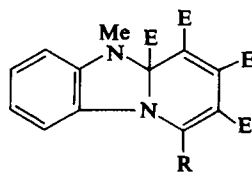


(357) R = H

(358) R = Et

(359) R = *t*-Bu

(360)

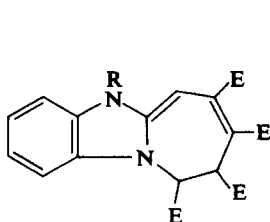


(361) R = H

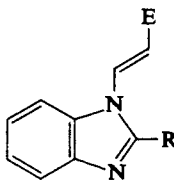
(362) R = Ph

by a [1,5] sigmatropic hydrogen shift, as in the *9aH*-quinolizine series, can give the other product (**360**). In the case of 2-ethyl-1-methylbenzimidazole in tetrahydrofuran, the unrearranged adduct **358** is the only product isolable^{134,138}; rearranged adducts (cf. **361**) and azepines (**363**) are also obtained from 1-ethyl-2-methyl- and 1,2-dimethylbenzimidazoles.^{134,138} 1-Methyl-2-isopropylbenzimidazole also appears to give an unrearranged adduct,²¹⁰ but the situation varies with benzimidazoles of type **364**.²¹⁰ Where R = *t*-butyl, the product loses the *t*-butyl group in the mass spectrometer to give the base peak, suggesting that it is at the 5*a*-position (**359**), but when R = Ph the product gave the molecular ion through loss of CO₂Me, which now suggests, in agreement with the ¹H NMR spectrum, that this compound is **362**.

The situation is more complex for **364** if R = methyl or benzyl, for then a series of compounds is formed. These have been described as as azepinobenzimidazoles,²¹⁰ but are probably cyclobuta[4,5]pyrrolo-[1,2-*a*]benzimidazoles (cf. **369** and compounds from DMAD and 2-methylquinoline). Minor products from these reactions may have structure **365**, and similar compounds have been obtained from 2-benzimidazolylacetonitrile and ethyl 2-benzimidazolylacetate.²⁰⁸

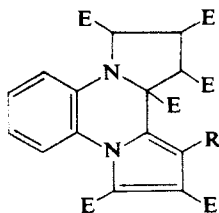


(363) R = Me or Et

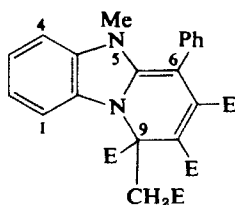


(364)

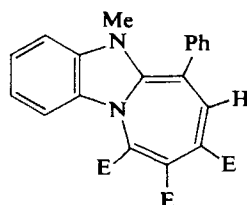
²¹⁰ R. M. Acheson and M. S. Verlander, *J. Chem. Soc., Perkin Trans. 1*, 430 (1974).



(365) R = H or Ph

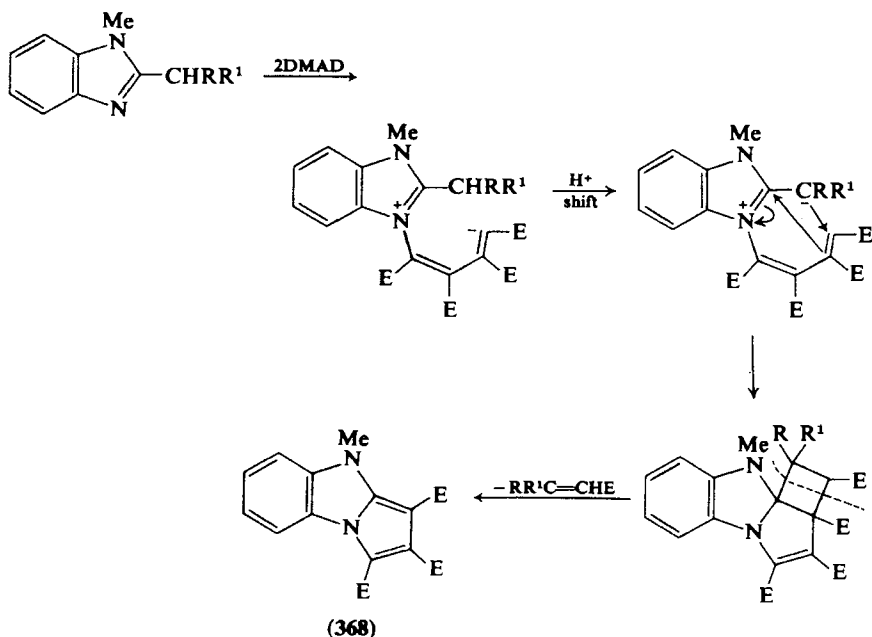


(366)



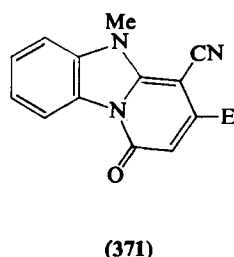
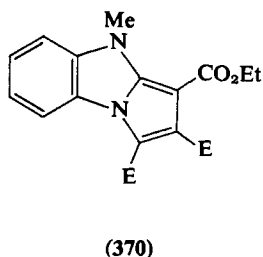
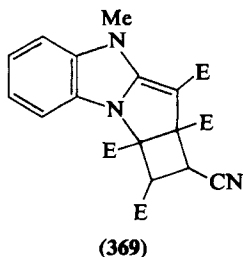
(367)

2-Benzyl-1-methylbenzimidazole gave five products with DMAD in acetonitrile.²⁰⁷ They include adducts corresponding to **358**, **363** (R = PhCH₂), **366**, **367**, and **368**. This last type of compound is also obtained, with other products, from a number of other benzimidazoles, and its formation is rationalized in Scheme 3.



SCHEME 3

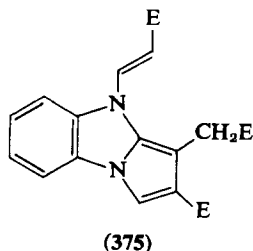
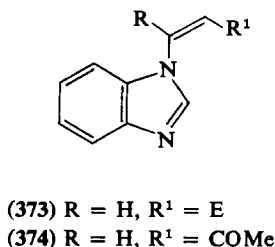
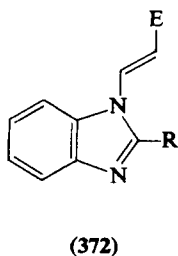
1-Methylbenzimidazoles with strongly activated methylene groups have been reacted with DMAD in acetonitrile. The 2-acetonitrile yields the 6-cyano analog of **366** and a compound considered to be an azepine but which is probably **369**, whereas the 2-ethoxycarbonylmethyl



derivative again gives the corresponding derivative to **368** and **370**.²⁰⁸ In dimethylformamide solution, however, the 2-acetonitrile (**349**, 1-Me) with DMAD is considered to give **371**.²⁰⁹

3. Benzimidazoles with MP

Benzimidazole, and many 2-substituted derivatives, with MP in acetonitrile give *E*-acrylates (e.g., **372**), but in methanol only the *Z*-isomer **373** is isolable from benzimidazole itself.²¹¹ Mixtures of **372** and **373** are

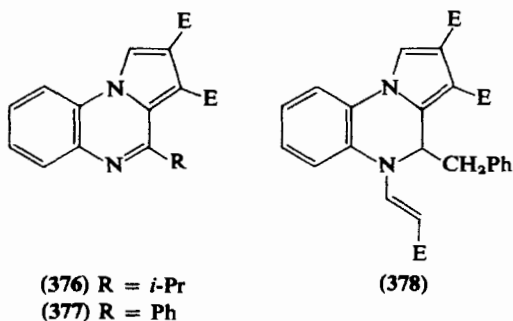


obtained using benzene, whereas benzimidazole with but-1-yn-3-one in this solvent yields the *Z* isomer **374**, which rearranges to the *E* compound (cf. **372**) faster than it can be isolated.²¹² Benzimidazole with MP at 120°, without solvent gives 30% of **372**, 2.5% of **373** and some pyrrolo-[1,2-*a*]benzimidazole (**375**).²¹¹ Heating MP alone with 2-isopropyl- and 2-benzylbenzimidazoles gave²¹¹ the tricyclic compounds **376** and **378**, respectively, along with *E*-acrylates (cf. **372**), whereas 2-phenylbenzimidazole gave only **377**.²¹¹ Various schemes have been suggested^{211,213} to account for the expansion of the benzimidazole to the quinoxaline system.

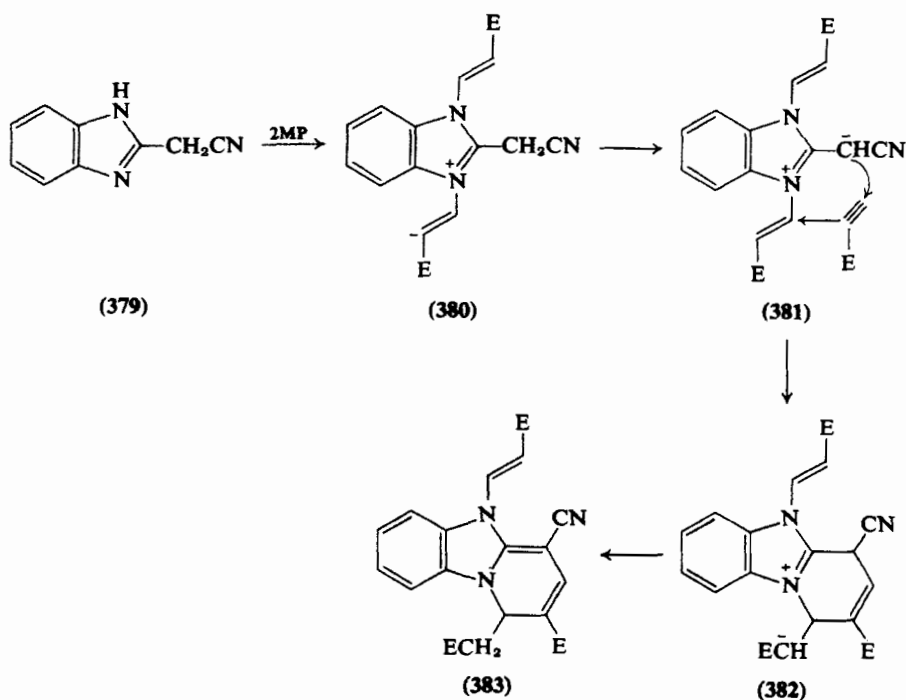
²¹¹ R. M. Acheson and M. S. Verlander, *J. Chem. Soc., Perkin Trans. 1*, 2348 (1973).

²¹² R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 446 (1975).

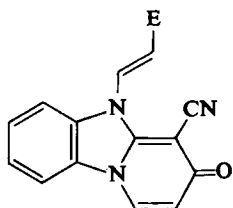
²¹³ M. S. Verlander, D. Phil. Thesis, Oxford, 1970, M.S. D.Phil. d. 5086.



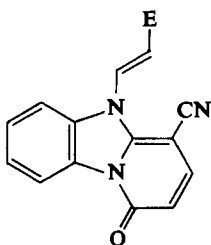
2-Benzimidazolylacetonitrile (379) with MP in refluxing acetonitrile gave 383, which could be formed via 380, 381 and 382 (Scheme 4), along with (384) and (385)²⁰⁸; compounds similar to 384 and 386 are formed from ethyl 2-benzimidazolylacetate.²⁰⁸ Methyl propiolate has also been reacted with the 1-methyl derivative of 379, and with ethyl 1-methyl-2-benzimidazolylacetate, to give *N*-methyl derivatives of the aforementioned types.²⁰⁸



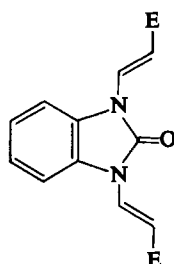
SCHEME 4



(384)



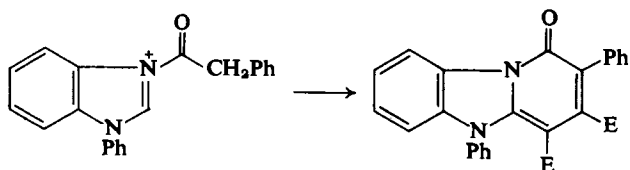
(385)



(386)

4. Miscellaneous Benzimidazoles with Acetylenic Esters

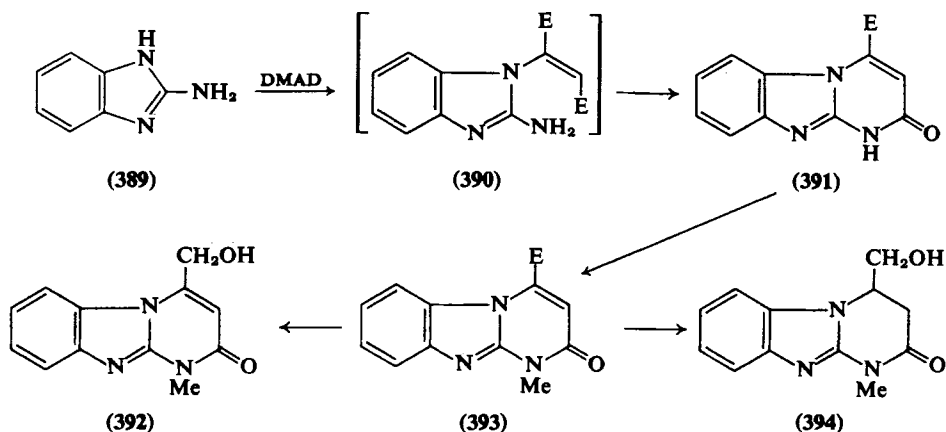
Addition of DMAD to the benzimidazolium salt **387** gave the cycloadduct **388**.²¹⁴



(387)

(388)

Several groups studied related reactions of 2-aminobenzimidazoles with compatible results. Troxler and Weber²¹⁵ added DMAD to 2-aminobenzimidazole (**389**); the major adduct **391** (a minor product was not identified) was methylated to give **393**, which was reduced by



(389)

(390)

(391)

(392)

(393)

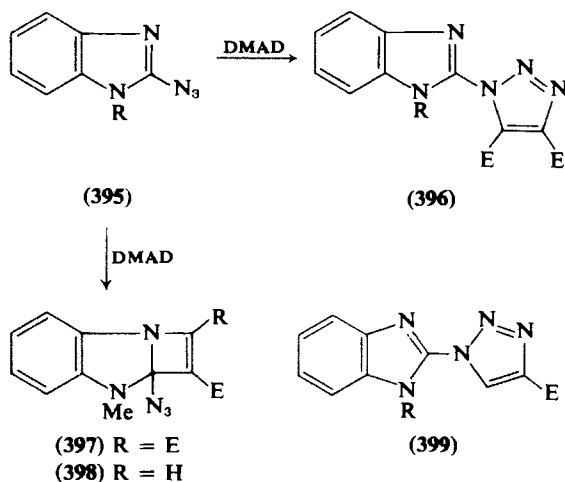
(394)

²¹⁴ N. F. Elmore, personal observation.

²¹⁵ F. Troxler and H.-P. Weber, *Helv. Chim. Acta* **57**, 2356 (1974).

sodium borohydride at 0° to **392** (53%) and **394** (28%). Similar additions of propiolic, phenylpropiolic, and tetrolic esters to a range of 2-amino-benzimidazoles including 1-methyl, 2-methyl, and 2-phenyl have been described.²¹⁶⁻²¹⁸

The addition of DMAD to 2-azidobenzimidazole (**395**) yielding **396** has been reported in a German patent²¹⁹; in acetonitrile the interesting azetine (**397**) was obtained. Methyl propiolate with **395** gave (**399**) and **398**.²²⁰ Reaction of 2-hydrazinobenzimidazole (**400**) with DMAD gave



the Michael-type adduct (**401**) which, on heating in methanol, cyclized to give mainly **403** with a trace of **402**.²²¹

Russian workers²²² reacted 2-mercaptobenzimidazole (**404**) with DMAD and MP and obtained **405** and **406**, respectively. The reaction with propiolic acid to give **407** has recently been described.²²³

²¹⁶ D. W. Dunwell and D. Evans, *J. Chem. Soc., Perkin Trans. I*, 1588 (1973).

²¹⁷ H. Ogura, M. Kawano, and T. Itoh, *Chem. Pharm. Bull.* **21**, 2019 (1973).

²¹⁸ A. W. Chow, D. R. Jakas, B. P. Trotter, N. M. Hall, and T. R. E. Hoover, *J. Heterocycl. Chem.* **10**, 71 (1973).

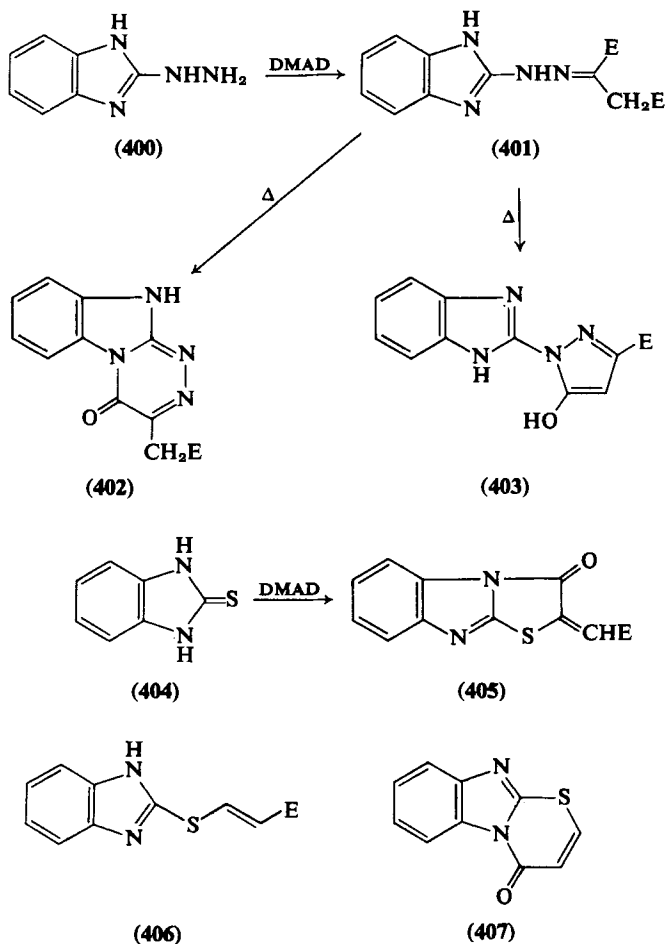
²¹⁹ E. Aufderhaar and A. Meyer, German Patent 2,263,879 [CA **79**, 78,815 (1973)].

²²⁰ Y. Shiokawa and S. Ohki, *Chem. Pharm. Bull.* **21**, 981 (1973).

²²¹ D. J. LeCount and A. T. Greer, *J. Chem. Soc., Perkin Trans. I*, 297 (1974).

²²² E. I. Grinblat and I. Ya. Postovskii, *Dokl. Akad. Nauk SSSR* **133**, 847 (1960) [CA **54**, 24,756 (1960)]; *Zh. Obshch. Khim.* **31**, 394 (1961) [CA **55**, 222,981 (1961)].

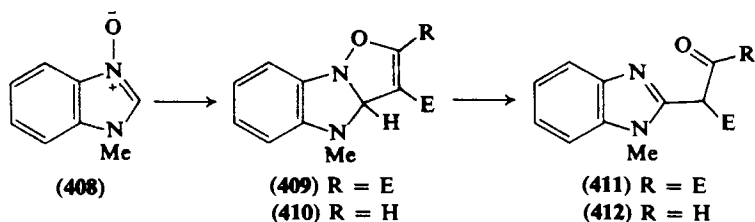
²²³ L. V. Zavyalova, N. K. Rozhkova, and K. L. Seitanidi, *Khim. Geterotsikl. Soedin.*, 47 (1975).



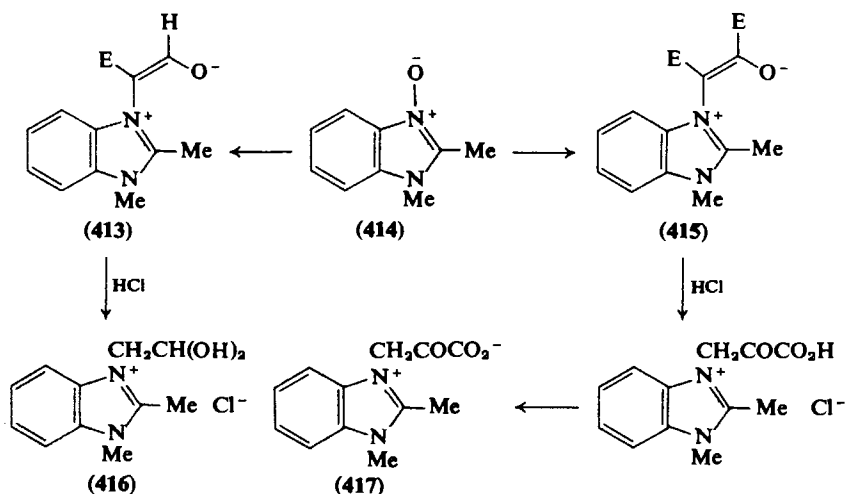
5. Benzimidazole Oxides

Acetylenic esters add to benzimidazole oxides which behave as 1,3-dipoles; the reactions take place vigorously at room temperature. From 1-methylbenzimidazole-3-oxide (**408**) and DMAD, Takahashi and Kano²²⁴ obtained **411** via the isoxazoline (**409**), whereas MP gave **412**. The reaction of 1,2-dimethylbenzimidazole-3-oxide (**414**) with DMAD the MP gave the benzimidazolium betaines **415** and **413** respectively;

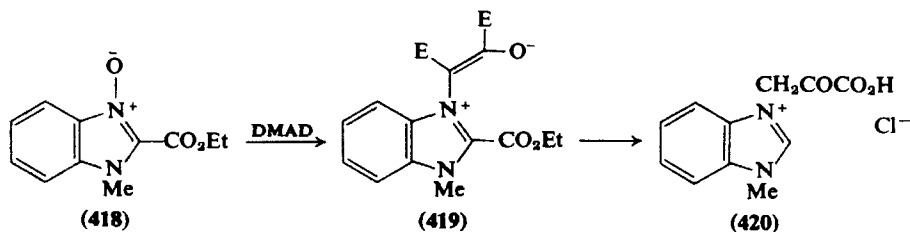
²²⁴ S. Takahashi and H. Kano, *Tetrahedron Lett.*, 1687 (1963); *Chem. Pharm. Bull.* **12**, 1290 (1964).



acid treatment of these two adducts gave **417** and **416** as shown. Alternative possible mechanisms for the formation of these compounds



were also discussed.²²⁵ 2-Ethoxycarbonyl-1-methyl-benzimidazole-3-oxide (**418**) with DMAD gave the betaine (**419**), which lost two carboxyl groups with hydrochloric acid forming **420**.²²⁶

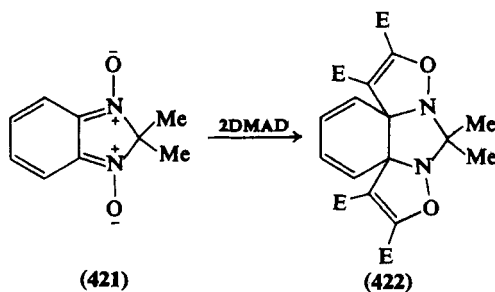


²²⁵ S. Takahashi and H. Kano, *J. Org. Chem.* **30**, 1118 (1965).

²²⁶ S. Takahashi and H. Kano, *Chem. Pharm. Bull.* **16**, 527 (1968).

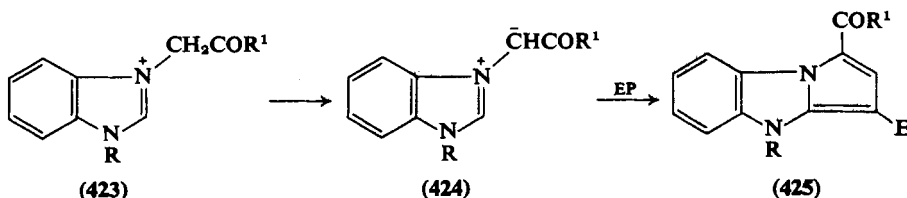
6. Isobenzimidazoles and Their Oxides

Isobenzimidazoles and their mono and di-*N*-oxides show no tendency to react in a Diels-Alder fashion with tetracyanoethylene or a wide range of other dienophiles. However, with DMAD in cold benzene, the di-*N*-oxide **421** gave a 1:2 adduct (**422**) whose structure was assigned on the basis of X-ray data.²²⁷



7. Benzimidazolium Ylids

Reaction of 3-substituted 1-alkylbenzimidazolium ylids (**423**) with EP gave²²⁸ pyrrolo[1,2-*a*]benzimidazoles (**425**).

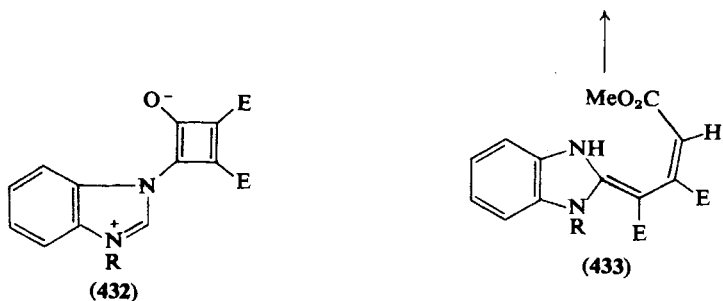
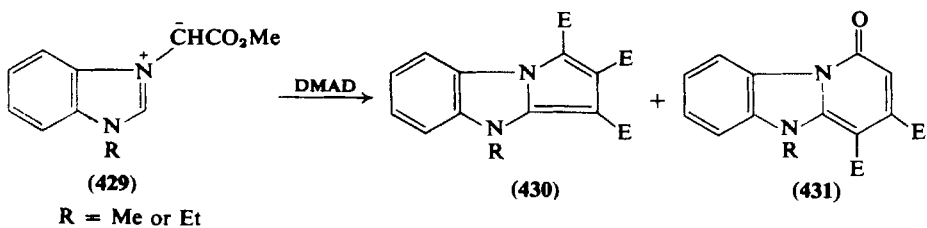
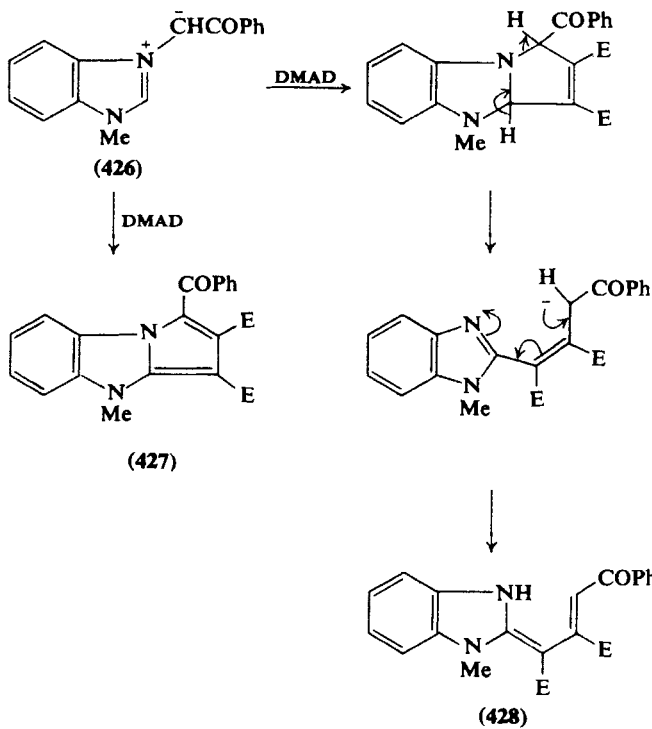


R = Me or Et
 R^1 = OMe, Ph, 4Br- C_6H_4

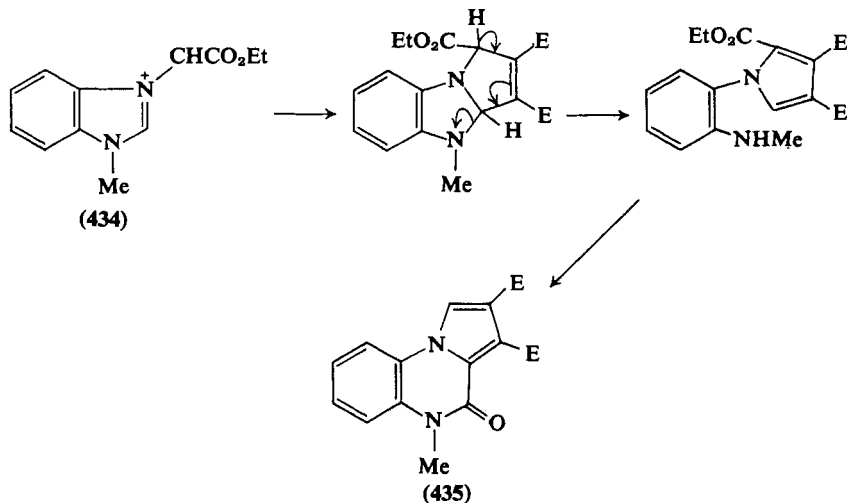
With DMAD, the phenacyl ylid (**426**) gave a low yield of **427** and the open-chain compound **428**. 1-Alkyl-3-methoxycarbonylmethylbenzimidazolium ylids (**429**) gave the "normal" products (**430**), and **431** which probably arises by cyclization of the corresponding open-chain (**433**) intermediate (cf. **428**).²²⁸ These reactions have also been investigated

²²⁷ D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. Herbert, *J. Chem. Soc., Perkin Trans. I*, 470 (1977).

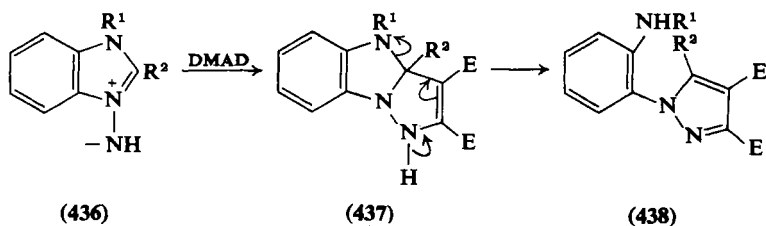
²²⁸ H. Ogura and K. Kikuchi, *J. Org. Chem.* **37**, 2679 (1972).



by Zugravescu and co-workers²²⁹ who obtained similar products but postulated cyclobutenone intermediates (**432**) from DMAD and **429** (Et ester, R = Me or CH₂Ph). Meth-Cohn²³⁰ reinvestigated the reaction of the ylid **434** with DMAD and concluded (¹³C NMR) that the products previously formulated as **432** are best represented by structure **435** and arise as shown.



1,3-Cycloadditions to 1-methylbenzimidazolium 3-imines (**436**) by reactions with DMAD in DMF in the presence of potassium carbonate gave 57% of the pyrazole **438** resulting from the cleavage of **437**.²³¹ The reaction took a different path when MP was added to the carbonyl-stabilized imine (**439**); the product **441** arises from **440**.²³²

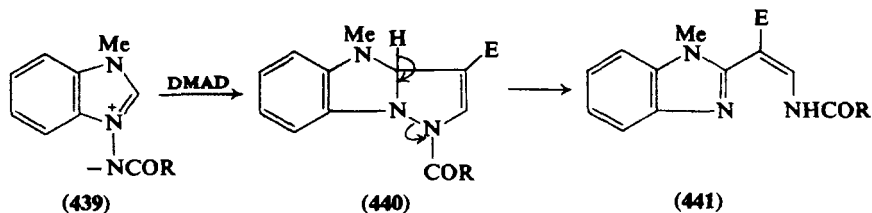


²²⁹ I. Zugravescu, J. Herdan, and L. Druta, *Rev. Roum. Chim.* **19**, 649 (1974) [*CA* **81**, 25,603 (1974)].

²³⁰ O. Meth-Cohn, *Tetrahedron Lett.*, 413 (1975).

²³¹ Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *Chem. Ind. (London)*, 952 (1973); *J. Heterocycl. Chem.* **12**, 225 (1975).

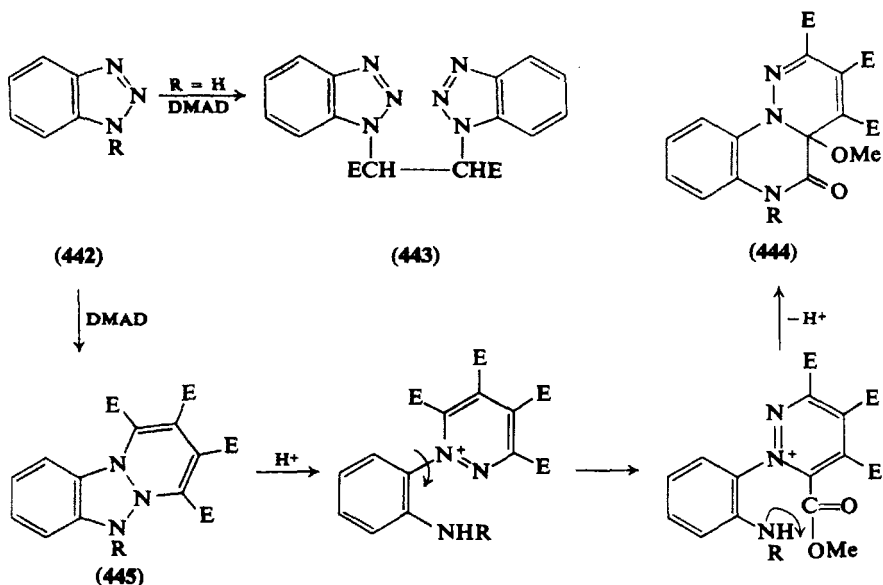
²³² Y. Tamura, H. Hayashi, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 819 (1975).



K. BENZOTRIAZOLES

1. Benzotriazoles with DMAD

Benzotriazole (**442**, R = H) with DMAD in acetonitrile gave the succinate **443**,²³³ but 1-methyl-, 1-ethyl-, and 1-benzylbenzotriazoles in tetrahydrofuran yield mixtures of deep red (**445**) and yellow (**444**) tricyclic compounds.²³⁴ The red compounds are isomerized by trifluoroacetic acid via a ring-opening-ring closure sequence involving attack from the alkylamino group at an ester carbonyl to the yellow isomers (**444**), which are the sole products isolable if the original reaction involving DMAD is carried out in ether or acetonitrile solution.²³⁴

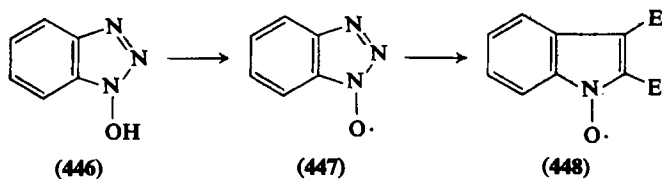


²³³ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 389 (1968).

²³⁴ P. J. Abbott, R. M. Acheson, M. W. Foxton, N. R. Raulins, and G. E. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 2182 (1972).

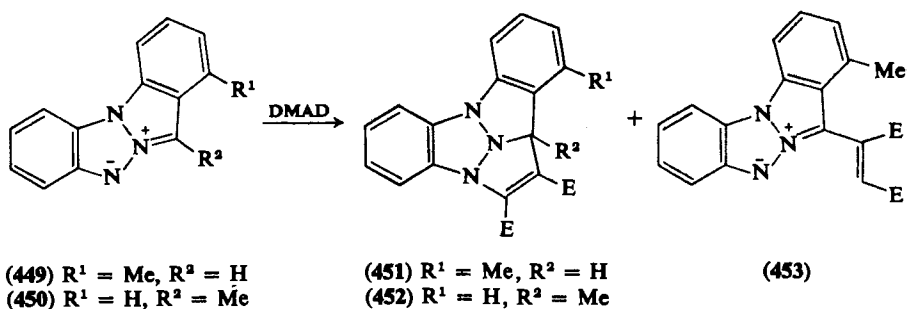
2. Benzotriazole 1-Oxide Radical with DMAD

Oxidation of 1-hydroxybenzotriazole (**446**) in the absence of oxygen gave the benzotriazole 1-oxide radical (**447**), which, on reaction with DMAD, evolved nitrogen and formed the new radical **448**.²³⁵



3. Dibenzotriazapentalenes

Dibenzotriazapentalenes (**449** and **450**) with DMAD and DEAD gave adducts **451** and **452**.²³⁶ The reactions with DMAD were solvent-depen-

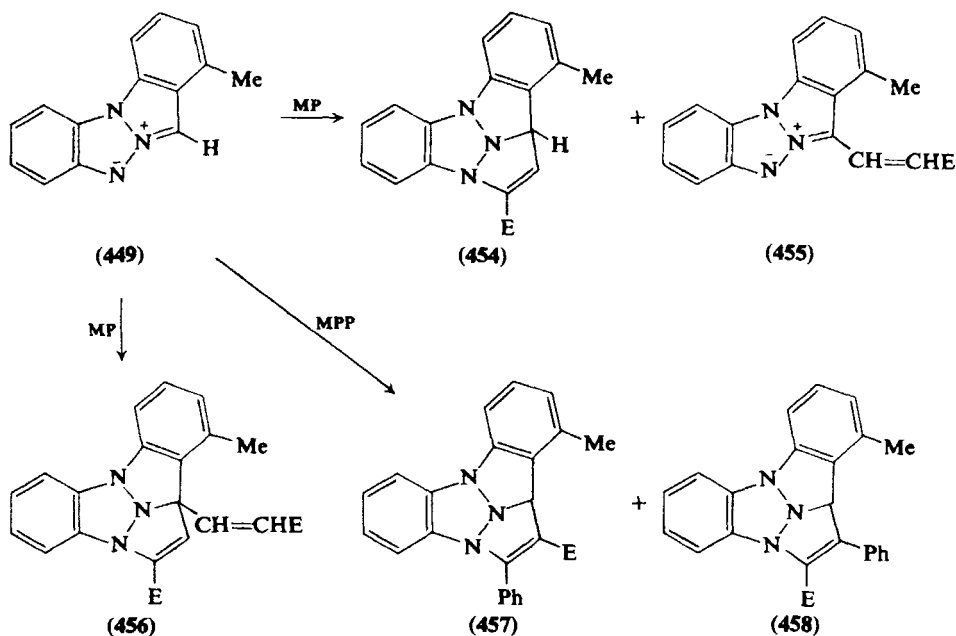


dent: **449** in methylene dichloride for 24 hours at 30° gave 32% of **451** and 1% of **453**, whereas heating in acidified ethanol gave 60% of **451** and 32% of **453**. Compound **450** gave 90% of **452** and no **453** in hot ethanol.²³⁷ Similar reaction of **449** with MP gave varying quantities of **454**, **455** and **456**, depending on the solvent used; MPP gave isomers **457** and **458**.

²³⁵ H. Gaurich and W. Weiss, *Chem. Ber.* 106, 2408 (1973).

²³⁶ O. Tsuge and H. Samura, *Tetrahedron Lett.*, 597 (1973).

²³⁷ O. Tsuge and H. Samura, *Heterocycles* 2, 27 (1974).



V. Compounds from Six-Membered Ring Heterocycles Containing Only Nitrogen as Heteroatom

A. PYRIDINES

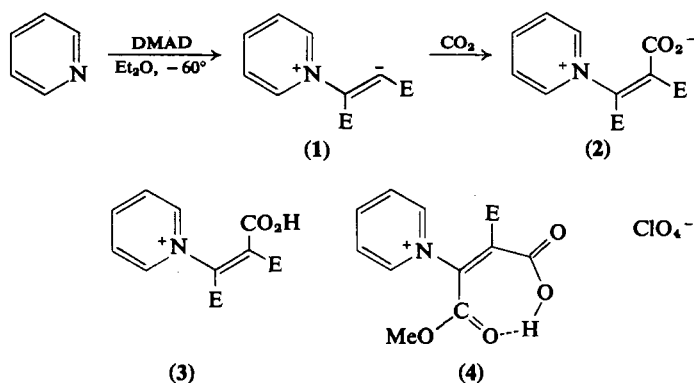
1. Pyridines with DMAD in Aprotic Solvents

When the nitrogen atom of a pyridine is sufficiently nucleophilic, for example 3-cyano- (pK_a 1.45) but not 3-bromopyridine (pK_a 0.9), attack occurs at the triple bond of the ester.²³⁸ The reaction can be very vigorous and, if carried out at -60° in ether, pyridine itself appears to yield the zwitterion **1** which can be trapped by carbon dioxide. No direct physical evidence has been obtained for **1** and the first product detectable by low-temperature NMR measurements is the 9a*H*-quinolizine **5**.²³⁹ Both geometrical forms of the betaine (**2**) have been isolated, and, at 0° in chloroform, decomposition to carbon dioxide, detected by its absorption at 2335 cm^{-1} , and a red tar, occur rapidly. Treatment of the betaines with aqueous perchloric acid at its freezing point, however,

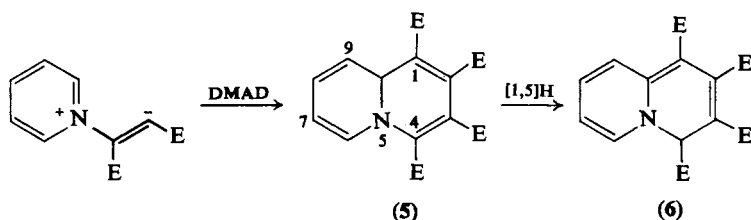
²³⁸ R. M. Acheson and D. A. Robinson, *J. Chem. Soc. C*, 1629 (1968).

²³⁹ R. M. Acheson, *Khim. Geterotsikl. Soedin.*, 1011 (1976).

gave the relatively stable perchlorates **3** and **4**,²⁴⁰ of which only the second shows a strong intramolecular hydrogen bond. 3-Methyl-, 3,5-, and 2,6-dimethylpyridine behave similarly.²⁴⁰



At 0°–25° pyridine, and many alkylpyridines, with 2 moles of DMAD in many solvents such as ether or benzene, or better in highly polar solvents such as nitromethane,²⁴¹ or preferably acetonitrile in which a lower proportion of red polymer is formed,^{242–244} give 9a*H*-quinolizines,



e.g., **5**. The 9a*H*-quinolizines could be formed by a stepwise, or concerted, cyclization and it has not been established which route is followed. 9a*H*-Quinolizine (**5**) was isolated by Diels and Alder in 1932, and although it can be detected as the first reaction product by NMR²³⁹ and has been isolated on one occasion since,²⁴⁵ rearrangement to the 4*H*-isomer **6** occurs very readily. The presence of alkyl groups can greatly stabilize

²⁴⁰ R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 2676 (1964).

²⁴¹ R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 438 (1975).

²⁴² R. M. Acheson and G. A. Taylor, *Proc. Chem. Soc.*, 186 (1959).

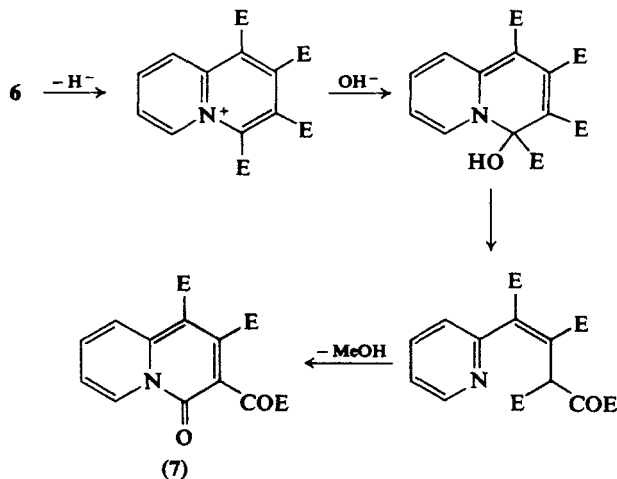
²⁴³ R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1691 (1960).

²⁴⁴ R. M. Acheson, J. M. F. Gagan, and G. A. Taylor, *J. Chem. Soc.*, 1903 (1963).

²⁴⁵ M. F. Lease, *Diss. Abstr.* **24**, 5000 (1964).

9a*H*-quinolizines, and a study of the isomerization of the 7,9-dimethyl derivative of **5** to the corresponding 4*H*-isomer (cf. **6**) has shown²⁴⁶ that it occurs by a [1,5] sigmatropic shift which takes place readily in hot toluene. Many alkyldiaryls yield quinolizines with DMAD; the unsymmetrically substituted mixtures, for example, 2-methylpyridine gives the 6- and 9a-methyl derivatives of **5**.^{247,248}

A common minor product in these reactions is exemplified by "Kashimoto's compound" (**7**), obtained from pyridine. It is probably formed as outlined²⁴⁹ from 4*H*-quinolizine (**6**) which must be oxidized. The formation of Kashimoto's compound may be due to the presence of trace impurities.



3-Cyanopyridine (pK_a 1.45) yields a trace of tetramethyl 9-cyano-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (cf. **5**) with DMAD; the only product isolable from the 4-cyano isomer was the trimethyl 7-cyanoindolizine-1,2,3-tricarboxylate (cf. **35**), whereas 2-methoxypyridine yielded **9** and **11**.²³⁸ Cyclization in one direction to give **8** followed by a [1,5] sigmatropic shift, and pericyclic ring opening would lead to **9**. The alternative cyclization to **10**, followed by ionization and recombination, or a [1,5] shift, gives a second product **11**, which has also been obtained from the quinolizinium salt **12**.

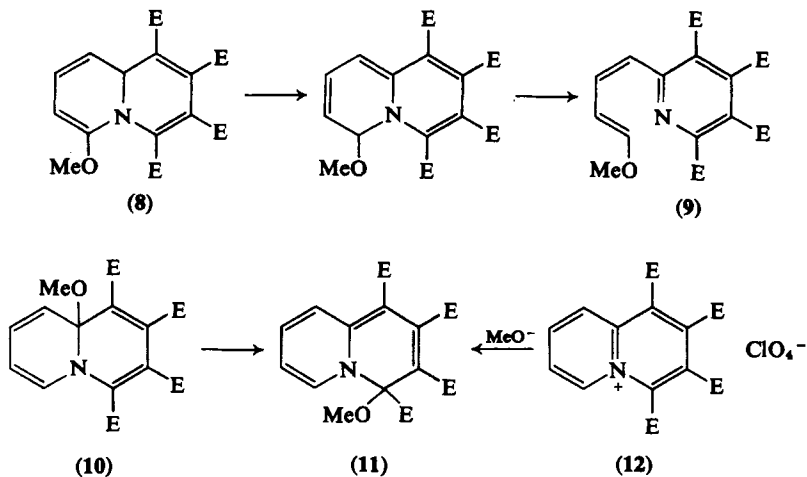
Although 2-vinylpyridine and its 6-methyl derivative with DMAD in

²⁴⁶ R. M. Acheson and B. J. Jones, *J. Chem. Soc. C*, 1301 (1970).

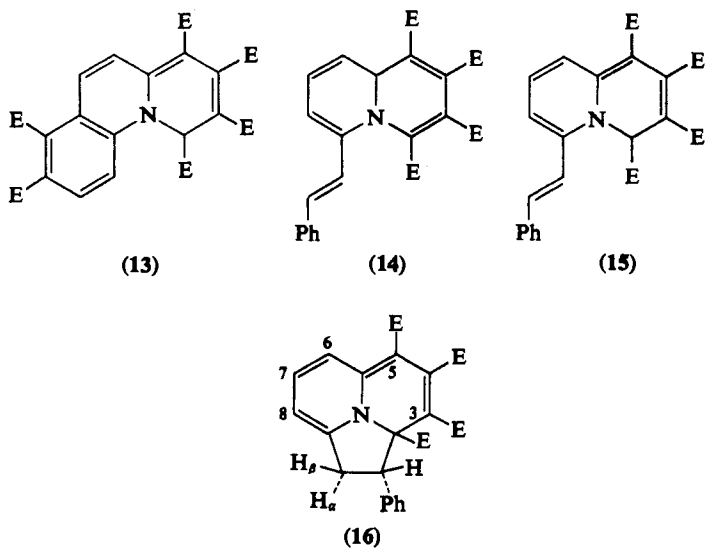
²⁴⁷ R. M. Acheson, J. M. F. Gagan, and R. S. Feinberg, *J. Chem. Soc.*, 948 (1965).

²⁴⁸ R. M. Acheson, M. W. Foxton, and A. R. Hands, *J. Chem. Soc. C*, 387 (1968).

²⁴⁹ R. M. Acheson, D. M. Goodall, and D. A. Robinson, *J. Chem. Soc.*, 2633 (1965).



acetonitrile give the expected quinolizines,²⁴⁸ and in the former case a small proportion of **13**, the formation of which is easily rationalized, *trans*-2-styrylpyridine (stilbazole) behaves a little differently.²⁵⁰ No 9a-styryl-9a*H*-quinolizine is isolable, but a mixture of **14**, **15**, and the [3,3,2]cyclazine (**16**) is formed. Cyclazine **16** is obtained from both **14** and **15** at 200°, but the best yield is obtained by refluxing the 9a*H*-

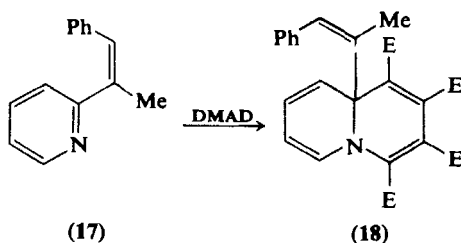


²⁵⁰ R. M. Acheson and R. S. Feinberg, *J. Chem. Soc. C*, 351 (1968).

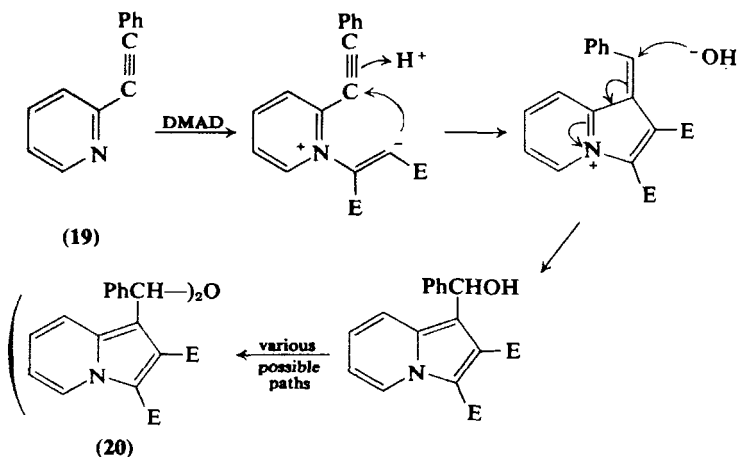
isomer **14** in acetic acid. The latter cyclization appears to proceed by addition of the proton appearing at the 1β - position of the cyclazine, cyclization, and loss of the bridgehead hydrogen atom; $4H$ -quinolizine (**15**) does not give the cyclazine **16** under these conditions.

cis-2-Styrylpyridine yields the *cis* isomer of **14** with DMAD, and on heating yields first the *cis*- $4H$ -isomer and, at higher temperatures, also the *trans*- $4H$ -isomer and a trace of cyclazine **16**.

Although 5-methyl-2-styrylpyridine gives a similar series of quinolizines and cyclazines, the only product isolable from **17** was the $9aH$ -substituted quinolizine (**18**).²⁵⁰



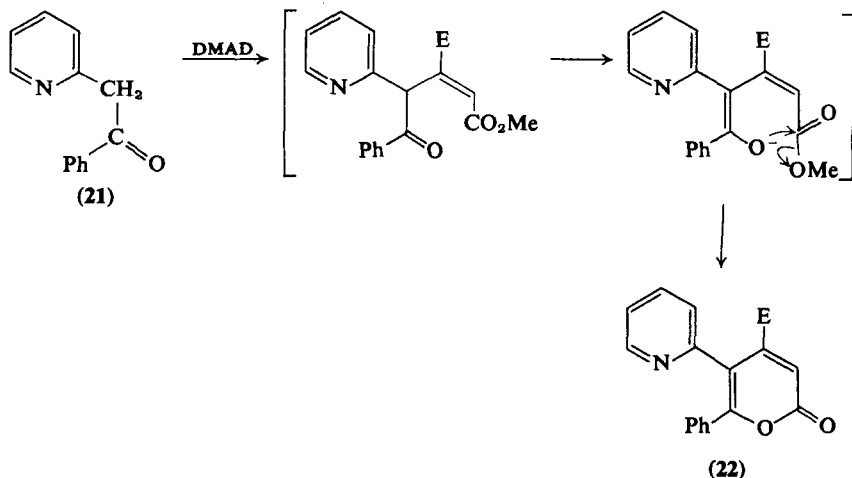
Attempts to extend the reactions to 2-phenylethynylpyridine (**19**), using not quite dry acetonitrile as solvent, gave only the ether (**20**).²⁵¹



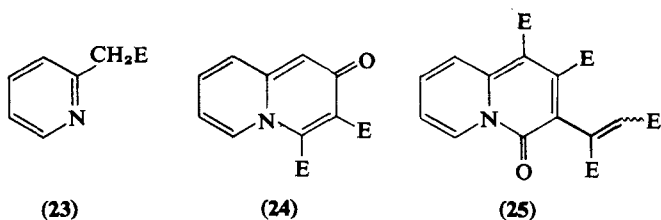
In contrast to the benzopyridines, alkyl groups attached to the 2-position of a pyridine ring are not sufficiently acidic to get involved in reactions with DMAD. However, if electron-attracting substituents are

²⁵¹ R. M. Acheson and J. N. Bridson, *J. Chem. Soc. C*, 1143 (1969).

present on the alkyl group, then the increased nucleophilic reactivity can even overcome that of the nitrogen atom. An example of this is the formation of the 2-pyrone **22** from **21**, occurring both in ether²⁵¹ and in *t*-butanol which possess a very weakly acidic proton. However, in the



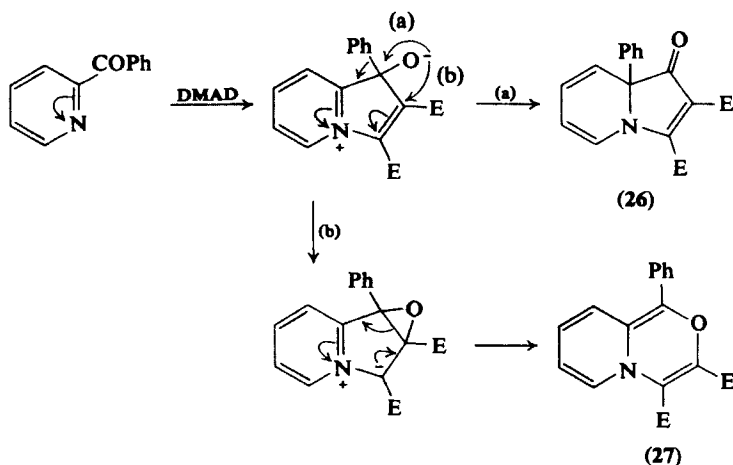
case of methyl pyridylacetate (**23**), a mixture of 2- (**24**) and 4-quinolizones (**25**) is obtained in ether²³⁸ and in *t*-butanol,²⁵² both with DMAD and DEAD. The 2-quinolizone must arise from nucleophilic attack from the nitrogen atom, and the 4-quinolizone from the methylene group.



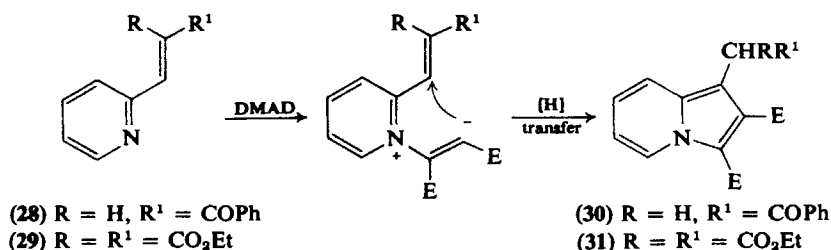
Treatment of 2-benzoylpyridine with DMAD gives mainly trimethyl indolizine-1,2,3-tricarboxylate, whose genesis is explained in the next section, and a 1:1 molar adduct that is considered²⁵³ to be formed by a phenyl migration and to have structure **26**. The evidence for this structure is quite unconvincing, and other structures such as **27** are more likely.

²⁵² E. Winterfeldt and A. Naumann, *Chem. Ber.* **98**, 3537 (1965).

²⁵³ E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.* **6**, 423 (1967).



The reaction of the 2-pyridylvinyl ketone **28** with DMAD could take place in several ways, but nucleophilic attack from the nitrogen and Michael-type addition to the conjugated system gives the indolizine **30**.²⁵¹ A similar cyclization occurs with the diethyl malonate derivative **29** yielding **31**, but in the case of **32** an unexpected rearrangement

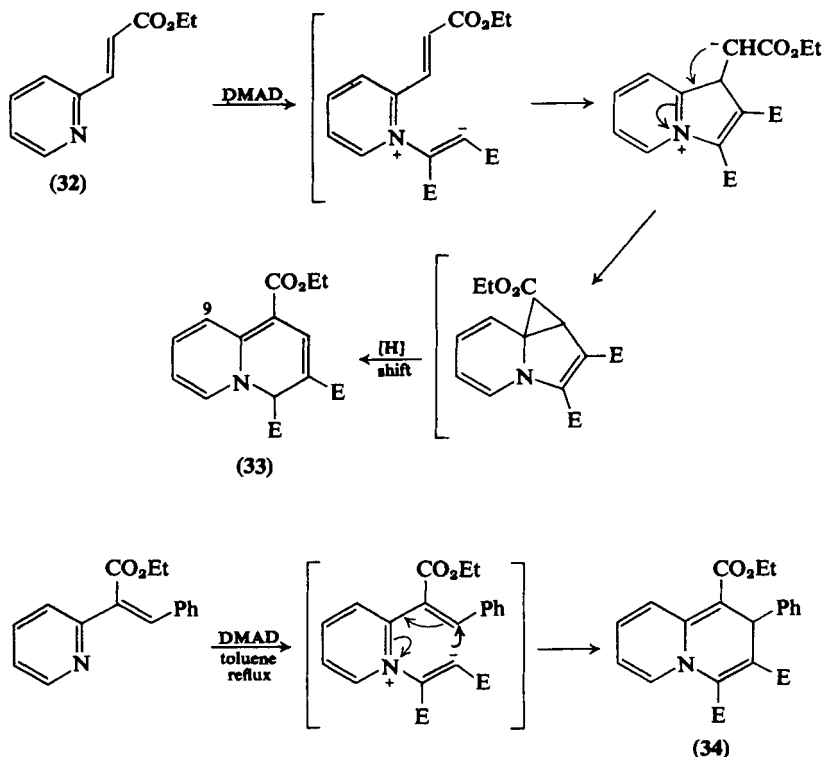


occurs as it does with the analogous quinoline.²⁵⁴ The identification of product **33** depends largely on the very low-field position of the 9-proton in the NMR spectrum; a similar product is obtained from EP but in very poor yield.

If the ester group is at the alternative position of the side chain, then the position of attack of the intermediate zwitterion is altered, leading to the first direct synthesis of 2*H*-quinolizines (e.g., **34**).²⁵⁵ Methyl propiolate gives only a trace of the corresponding 2*H*-quinolizine.

²⁵⁴ R. M. Acheson and J. M. Woollard, *J. Chem. Soc. C*, 3296 (1971).

²⁵⁵ R. M. Acheson, S. J. Hodgson, and R. G. M. Wright, *J. Chem. Soc., Perkin Trans. I*, 1911 (1976).

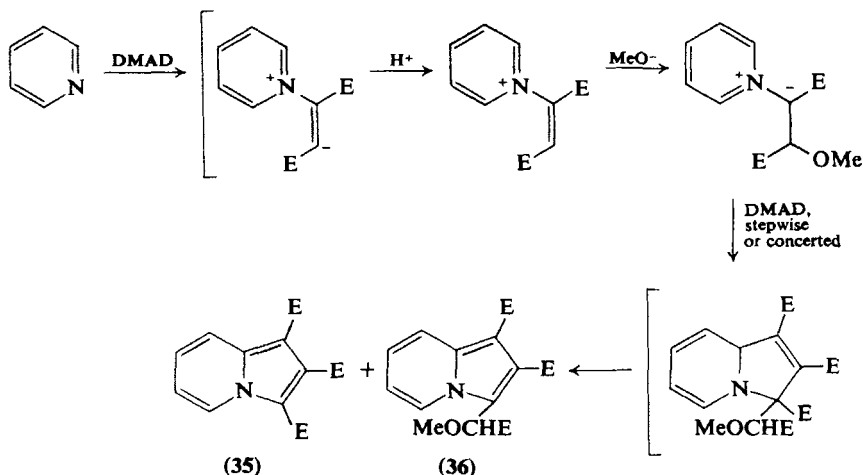


2. Pyridines with DMAD in Protic Solvents

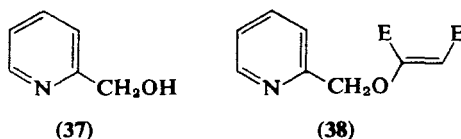
The effect of the presence of traces of water, or proton-donating solvents, on the reaction of DMAD with pyridines depends very much on the particular reaction conditions. For instance, 3,5-dimethylpyridine in dimethyl sulfoxide, containing 1 molar equivalent of water at 15% concentration, which presumably strongly interacts with the main solvent, gave a 65% yield of the pure 9a*H*-quinolizine (cf. 5) but 2-phenylethynylpyridine, under conditions designed to exclude water, gave the ether 20.²⁵⁴ The products obtained from pyridine^{256,257} and alkyipyridines^{243,254,257} using methanol as solvent are indolizines. Both 35 and 36 are obtained in the case of pyridine, while often only the indolizine-1,2,3-tricarboxylate (35) is isolable.

²⁵⁶ O. Diels and R. Meyer, *Annalen* **513**, 129 (1934).

²⁵⁷ A. Crabtree, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 3497 (1961).

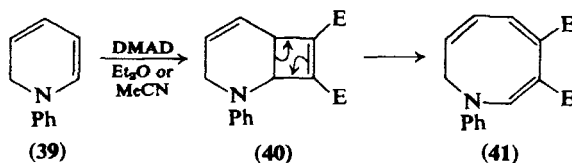


2-Pyridylmethanol (37) in ether reacts at the oxygen atom with DMAD to produce 38.²⁵⁴



3. Reduced Pyridines with DMAD

Some 1,2-dihydropyridines (e.g., 39) react like enamines rather than butadienes with DMAD and, subsequently, undergo ring expansion to dihydroazocines (41).^{258,259} In the case shown, the intermediate cyclobutene (40) has been detected by NMR spectroscopy. The reaction proceeds if the 1-substituent is styryl²⁶⁰ and also if 3-cyano or 3-carbamoyl groups are present.

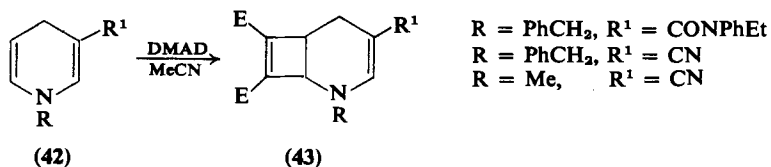


²⁵⁸ R. M. Acheson and G. Paglietti, *Chem. Commun.*, 665 (1973).

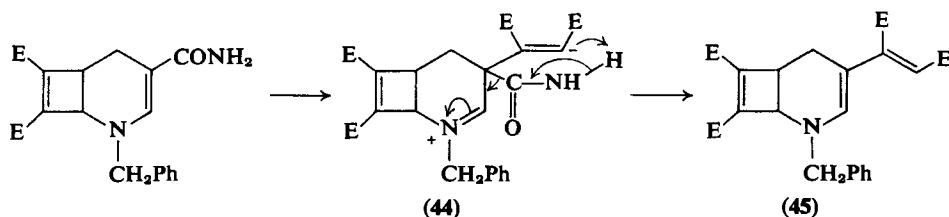
²⁵⁹ R. M. Acheson, G. Paglietti, and P. A. Tasker, *J. Chem. Soc., Perkin Trans. 1*, 2496 (1974).

²⁶⁰ P. S. Mariano, M. E. Osborne, and E. Krochmal, *Tetrahedron Lett.* 2741 (1975).

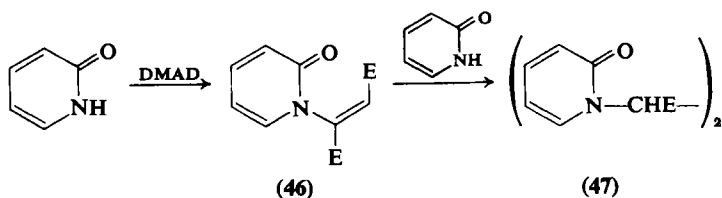
1,4-Dihydropyridines (42) behave in a similar way except that the initially formed four-membered ring (43) does not open under the influence of either heat or light in the cases examined.²⁶¹ If the 3-substituent of the dihydropyridine 42 is a carboxyl group, or a primary or a



secondary carboxamide, then a most interesting further reaction occurs through a six-membered transition state (44) with the elimination of carbon dioxide, or isocyanate, leading to the maleate derivative 45. The four-membered ring is probably formed before the elimination of the amide group occurs.²⁶¹



2-Pyridone undergoes Michael-type addition to DMAD, yielding 46 and the corresponding succinate 47.²⁶² Many reactions of this type were



reported subsequently,^{263,264} and where approach to the nitrogen atom of the 2-pyridone is sterically hindered, for example in the 4,6-dimethyl

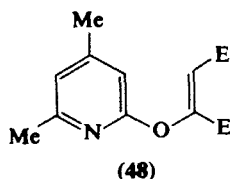
²⁶¹ R. M. Acheson, N. D. Wright, and P. A. Tasker, *J. Chem. Soc., Perkin Trans. 1*, 2918 (1972).

²⁶² R. M. Acheson and P. A. Tasker, *J. Chem. Soc. C*, 1542 (1967).

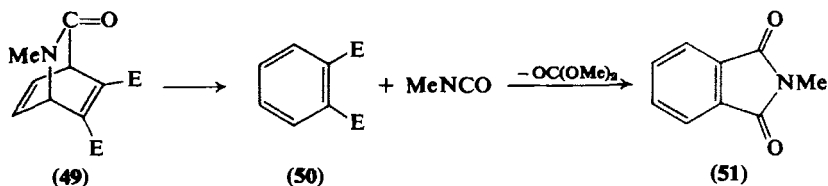
²⁶³ N. P. Shusherina, O. V. Slavyanova, G. N. Rodionava, and R. Ya. Levina, *Khim. Geterotsikl. Soedin.*, 489 (1970) [*CA* 73, 109,639 (1970)].

²⁶⁴ N. P. Shusherina and L. V. Betaneli, *Khim. Geterotsikl. Soedin.*, 1247 (1974) [*CA* 82, 16,664 (1975)].

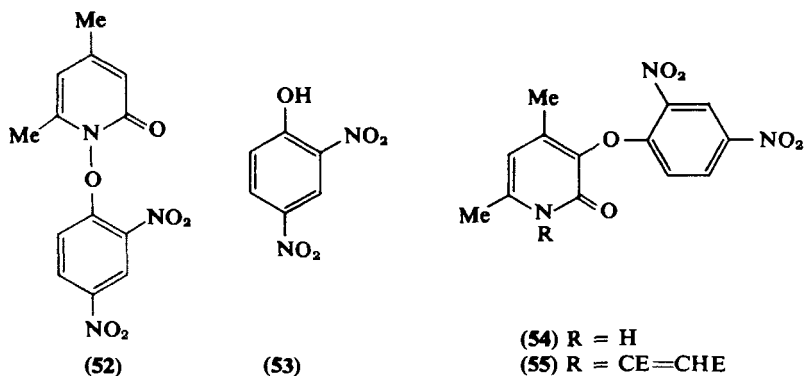
and 6-isopropyl-4-methyl derivatives addition occurs both at nitrogen, giving analogs of **46**, and at oxygen, yielding, for example, **48**.²⁶⁵



Recently, it has been shown that 2-pyridones with the nitrogen atom substituted by alkyl,²⁶² aryl, or methoxyl²⁶⁵ do undergo Diels-Alder reactions. Heating 1-methyl-2-pyridone with DMAD to 195°, the first successful example studied,²⁶² gave **51**, which was thought to be formed via **49** as shown. Under milder conditions,²⁶⁵ Diels-Alder adducts (cf. **49**) can be isolated and, on further heating, yield phthalic esters and isocyanates.

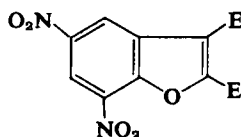


However when **52** was heated in benzene for 24 hours with DMAD five products (**53–57**) were identified, none of which is derived from a straightforward cycloaddition.²⁶⁶

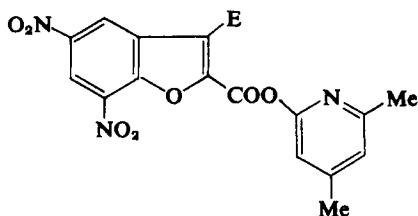


²⁶⁵ U. Heep, *Tetrahedron* **31**, 77 (1975).

²⁶⁶ N. Dennis, A. R. Katritzky, and Y. Takeuchi, *Angew. Chem., Int. Ed. Engl.* **15**, 1 (1976).

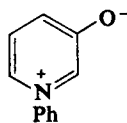


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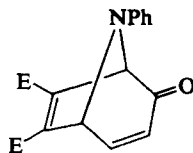


(57)

The cycloaddition of acetylenic esters (e.g., DMAD) to betaines (e.g., **58**) derived from 3-hydroxypyridine gives 1:1-molar adducts (e.g., **59**), and has been reviewed.²⁸⁶

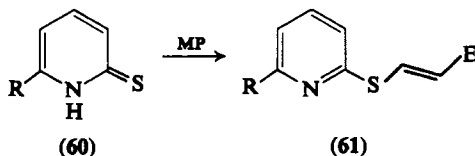


(58)



(59)

Undheim and Riege²⁸⁷ obtained 1:1 adducts from pyridine-2-thiones (**60**) and acetylenic amides, esters, and ketones. The reaction rate increases with increase in activation of the acetylenic bond by the adjacent carbonyl group and is affected by the pyridine 6-substituent, which may also affect the stereochemical course. Product-isomer ratios corresponding to kinetic control were obtained in chloroform. Amides gave *E* isomers, ketones gave *Z*, and esters a slight preponderance of the *E* isomers (**61**). Successive addition of *n*-butyllithium and DMAD to



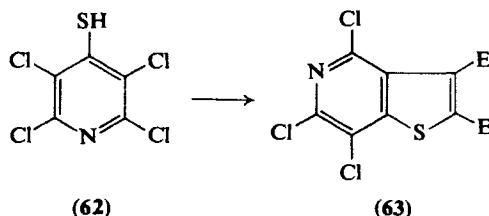
(60)

(61)

62 in THF gave dimethyl 4,6,7-trichlorothieno[3,2-*c*]pyridine-2,3-dicarboxylate (**63**).²⁸⁸

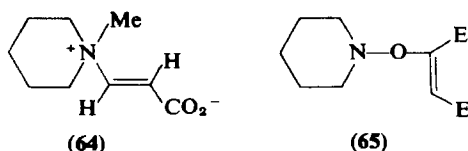
²⁸⁷ K. Undheim and L. A. Riege, *J. Chem. Soc., Perkin Trans. I*, 1493 (1975).

²⁸⁸ B. Iddon, H. Suschitzky, A. W. Thompson, and E. Ager, *J. Chem. Soc., Perkin Trans. I*, 2300 (1974).

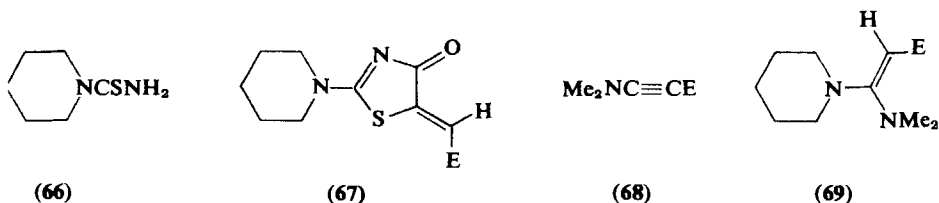


4. Piperidine and Derivatives

Addition of piperidine to acetylenic esters is, surprisingly, asserted to be independent of both solvent and base.²⁶⁹ *N*-Methylpiperidine adds to MP in highly aqueous media giving the betaine **64**.²⁷⁰ Winterfeldt and Krohn²⁷¹ added *N*-hydroxypiperidine to DMAD and obtained the single adduct **65**.



Piperidine thiourea (**66**) gave **67** with DMAD.²⁷² Piperidine has been added to the "push-pull" acetylene **68** giving **69**; rate studies have been reported.^{273,274}



The addition of DMAD and DEAD to triacetoneamine (**70**) in ether or hexane for 24 to 36 hours at 20° gave 58–70% yields of adducts **71**.²⁷⁵

²⁶⁹ E. Winterfeldt and H. Preuss, *Angew. Chem., Int. Ed. Engl.* **4**, 689 (1965).

²⁷⁰ A. W. McCulloch and A. G. McInnes, *Can. J. Chem.* **52**, 3569 (1974).

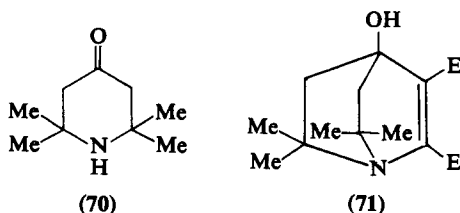
²⁷¹ E. Winterfeldt and W. Krohn, *Chem. Ber.* **102**, 2336 (1969).

²⁷² A. F. Cameron, N. J. Hair, N. F. Elmore, and P. J. Taylor, *Chem. Commun.*, 890 (1970).

²⁷³ A. Niederhauser, A. Frey, and M. Neuenschwander, *Helv. Chim. Acta* **56**, 944 (1973).

²⁷⁴ M. Neuenschwander and P. Bigler, *Helv. Chim. Acta* **56**, 959 (1973).

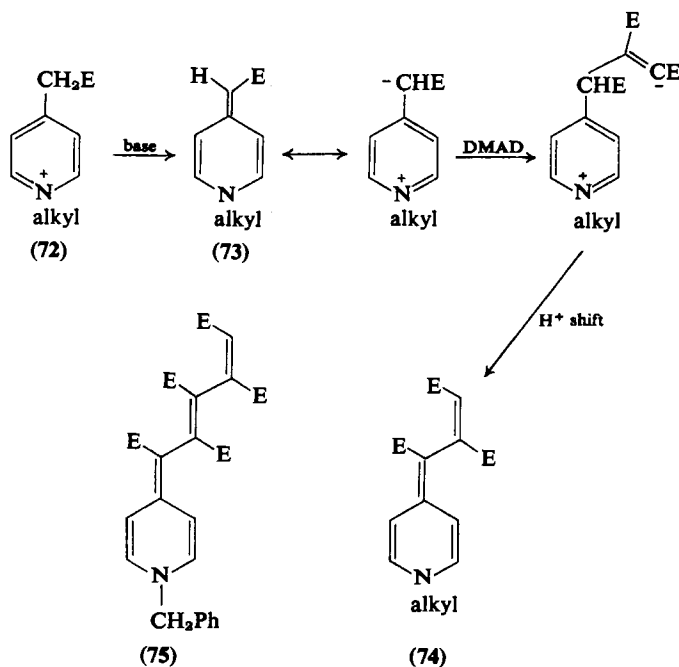
²⁷⁵ R. G. Kostyanovskii, Z. E. Samoilova, and M. Zarifova, Russian Patent 421–693 (1972), [*CA* **81**, 3782 (1974)].



Patents state that the addition products from 2,2,6,6-tetramethylpiperidin-4-ol and tetrolic acid are heat and light stabilizers for polymers.^{276,277}

5. Pyridine-Derived Enamines and Related Ylids with Acetylenic Esters

Pyridinium salts with activated methylene groups, such as **72**, give with bases the corresponding enamines **73**. A considerable number of these with DMAD, DEAD, and MP, give similar adducts (**74**).²⁷⁸

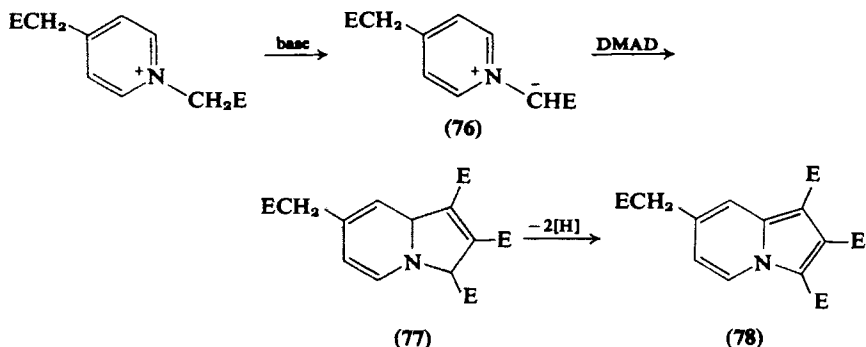


²⁷⁶ K. Murayama, S. Morimura, T. Yoshioka, and T. Kurumada, German Patent 2,352,606 [CA 81, 170,586 (1974)].

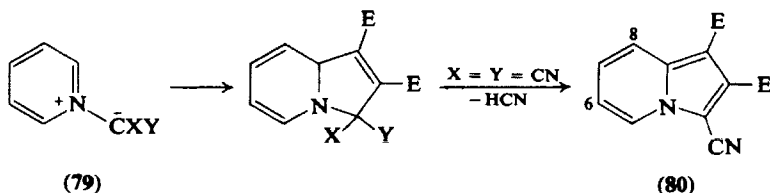
²⁷⁷ K. Murayama, S. Morimura, T. Yoshioka, and T. Kurumada, German Patent 2,365,369 [CA 82, 18,009 (1975)].

²⁷⁸ R. M. Acheson and J. M. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 744 (1975).

In a few cases 1:2 molar adducts such as **75** are formed.²⁷⁸ If the pyridine can form an ylid such as **76**, then an alternative cyclization to an indolizine (**78**) takes place to some extent.²⁷⁸ Many pyridinium ylids corresponding to **76**, but not possessing an ionizable proton at the 2- or



4-position, with DMAD^{279,280} and other activated acetylenes²⁸¹ and allenes,²⁸¹ give indolizines corresponding to **78** in good yield. The intermediate dihydroindolizines (cf. **77**) have been detected in a few instances, but usually aromatization occurs so rapidly as to preclude this. Another example is the ylid (**79**; X,Y = CN) obtained from pyridine with tetracyanoethylene oxide, which, with DMAD in acetonitrile at room temperature, gives a 48% yield of **80**.²⁸²



A study²⁸³ of the cyclization of 3-methyl derivatives of **79**, where X = Y = CN and X = H and Y = CPh, has been made. Hydrogen, or cyanide, was always lost at the aromatization stage. Inseparable mixtures of 6- and 8-methylindolizines were obtained in ca 1:3 ratio,

²⁷⁹ V. Boekelheide and K. Fahrenholz, *J. Am. Chem. Soc.* **83**, 458 (1961).

²⁸⁰ T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron* **28**, 4947 (1972).

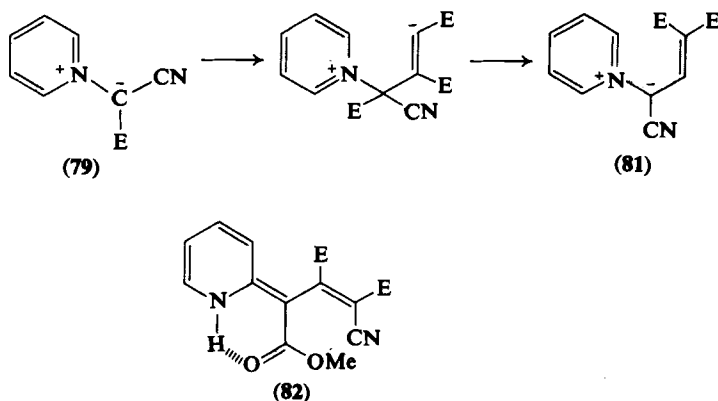
²⁸¹ R. M. Acheson, M. G. Bite, and M. W. Cooper, *J. Chem. Soc., Perkin Trans. I*, 1908 (1976).

²⁸² W. J. Linn, O. W. Webster, and R. A. Benson, *J. Am. Chem. Soc.* **87**, 3651 (1965).

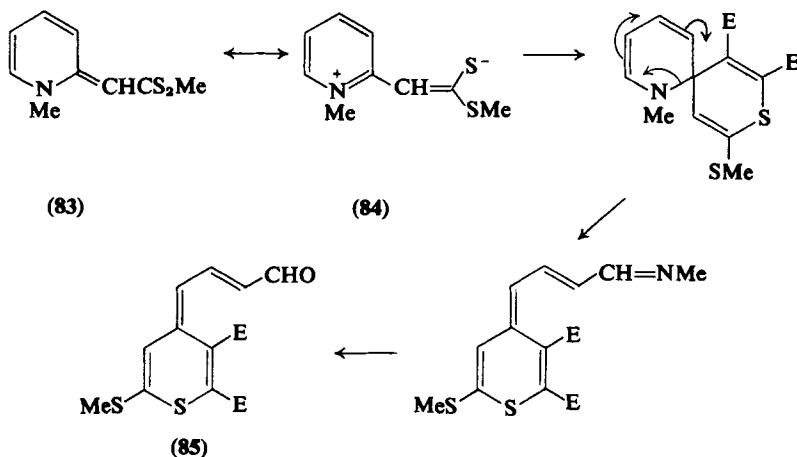
²⁸³ T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.* **37**, 813 (1971).

indicating that electronic, and not steric, factors control the mode of cyclization.

The course of the reaction between DMAD and alkoxy carbonyl-cyanopyridinium methylides (**79**; $X = \text{CN}$, $Y = \text{CO}_2\text{R}$) is strongly solvent dependent.²⁸⁴ In dimethylformamide or benzene, indolizines (e.g., **80**) are obtained, but in acetonitrile the reaction is stated to give **81**, an ester shift²⁸⁵ having taken place. Douglass and Wesolosky²⁸⁶ reacted the ylids **79** ($X = \text{E}$, $Y = \text{CN}$) with DMAD and isolated **82**.



The dithioester **83**, which can be written as an ylid (**84**), with DMAD alone at 100° , gave 10% of **85**.²⁸⁷ The nitrogen analog **86** apparently



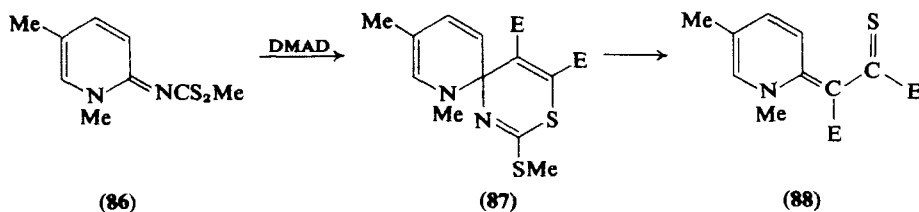
²⁸⁴ C. Leone and I. Zugravescu, *Tetrahedron Lett.*, 2029 (1972).

²⁸⁵ R. M. Acheson, *Acc. Chem. Res.* **4**, 177 (1971).

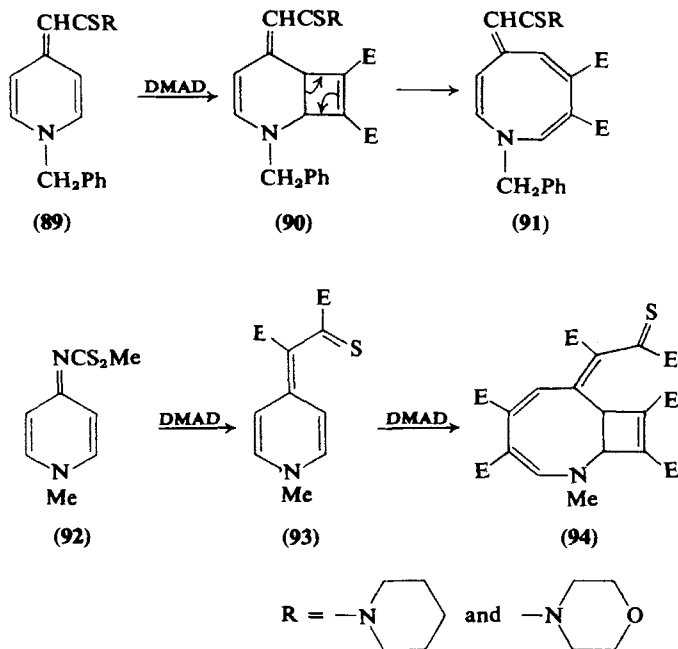
²⁸⁶ J. E. Douglass and J. M. Wesolosky, *J. Org. Chem.* **36**, 1165 (1971).

²⁸⁷ Y. Tominaga, K. Mizuyama, and G. Kobayashi, *Chem. Pharm. Bull.* **22**, 1670 (1974).

undergoes a similar addition to give a spiro intermediate (87), but then the reaction takes a different course to give 88 with the elimination of methyl thiocyanate.²⁸⁸



1-Benzyl-1,4-dihydropyridine derivatives (89) behave in rather different fashion and undergo ring expansion to the azacyclooctatetraene derivatives (91).²⁸⁹ This presumably occurs through cyclobutene (90), which ring-opens, in contrast²⁶¹ to corresponding cyclobutenes derived from simpler 1,4-dihydropyridines. Showing yet another behavior, the



²⁸⁸ K. Mizuyama, *Heterocycles* 4, 705 (1976).

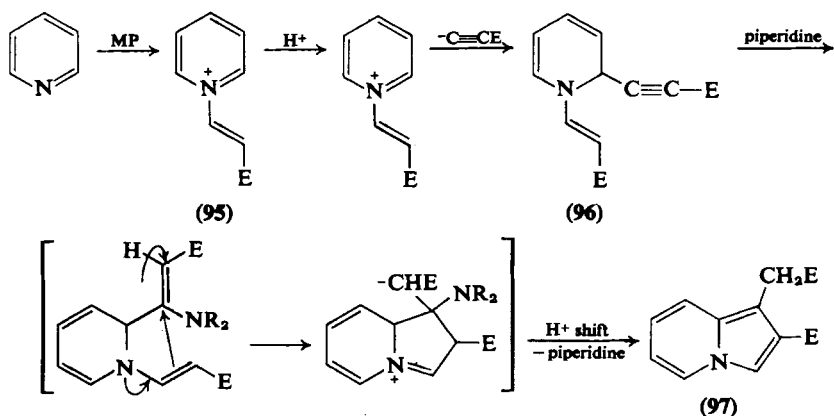
²⁸⁹ G. Kobayashi, Y. Matsuda, Y. Tominaga, and K. Kizuyama, *Chem. Pharm. Bull.* 23, 2749 (1975).

ester **92** behaves²⁸⁸ like **86** in its initial reaction with DMAD to give **93**. This compound undergoes a ring expansion and a further enamine-type addition with 2 moles more of DMAD to give **94**.

6. Pyridines with Propiolic Esters

Propiolic esters combine readily with pyridines to give first a zwitterion of type **95**, but the only recorded case of subsequent addition of a second mole of the ester to give a quinolizine is with 6-methylphenanthridine (see Section V,M). Zwitterion **95** usually abstracts a proton from either another molecule of alkyl propiolate or an alternative proton donor, and further reactions ensue. Some of the reactions are very difficult to reproduce and are very dependent on trace impurities and yield complex mixtures.

Pyridine with MP in ether was first reported²⁹⁰ to give dihydropyridine **96**, presumably by the sequence shown; subsequently only products derived from **96** were obtained.²⁹¹ Later, 3,5-dimethylpyridine in five experiments out of seven gave the corresponding dimethyl derivative of **96**.²⁹² Two types of indolizines, and [3,2,2]cyclazines, are also obtained



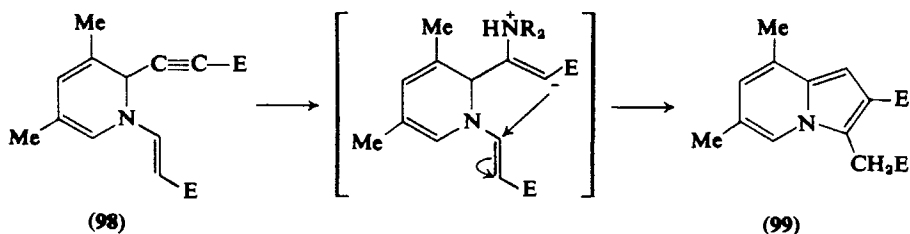
in these reactions,^{291,292} and it is likely that 1,2-dihydropyridines such as **96** are intermediates. Heating **96** with piperidine gives the indolizine **97**²⁹⁰ and several schemes could account for this. Indolizines of this type have been isolated from alkylpyridines and propiolic esters.²⁹¹ By contrast, the acetylene derivatives **98**, corresponding to **96**, but derived

²⁹⁰ A. Crabtree, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 3497 (1961).

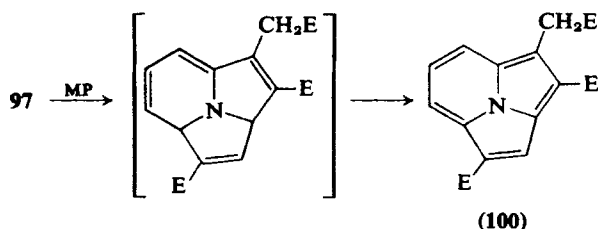
²⁹¹ R. M. Acheson and D. A. Robinson, *J. Chem. Soc. C*, 1633 (1968).

²⁹² R. M. Acheson and J. M. Woollard, *J. Chem. Soc. C*, 3296 (1971).

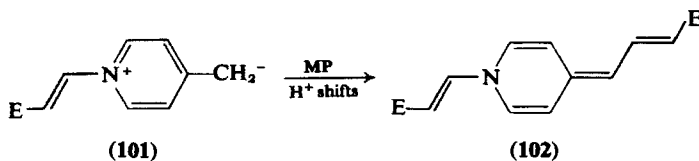
from 4-methyl-²⁹⁰ and 3,5-dimethylpyridine,²⁹² with piperidine in ether, cyclize in an alternative way to give a different type of indolizine **99**. Both types of cyclization can take place concurrently.



Other products from pyridine and its 3- and 4-methyl and 3,5-dimethyl derivatives and MP are cyclazines (e.g., **100**),²⁹¹ which are probably formed from indolizines of type **97** by further reaction with MP and subsequent aromatization. This type of reaction has been achieved by heating appropriate indolizines with DMAD²⁹³ or MP in the presence of palladized charcoal, and the direction of the addition, as shown below, has been established in several instances.²⁹⁴ Heating MP with diethyl-2-pyridylmethylene malonate gave the pyrrolo[2,1,5-*cd*]indolizine corresponding to **100**, no trace of the expected indolizine intermediate (cf. **97**) being observed.²⁹²



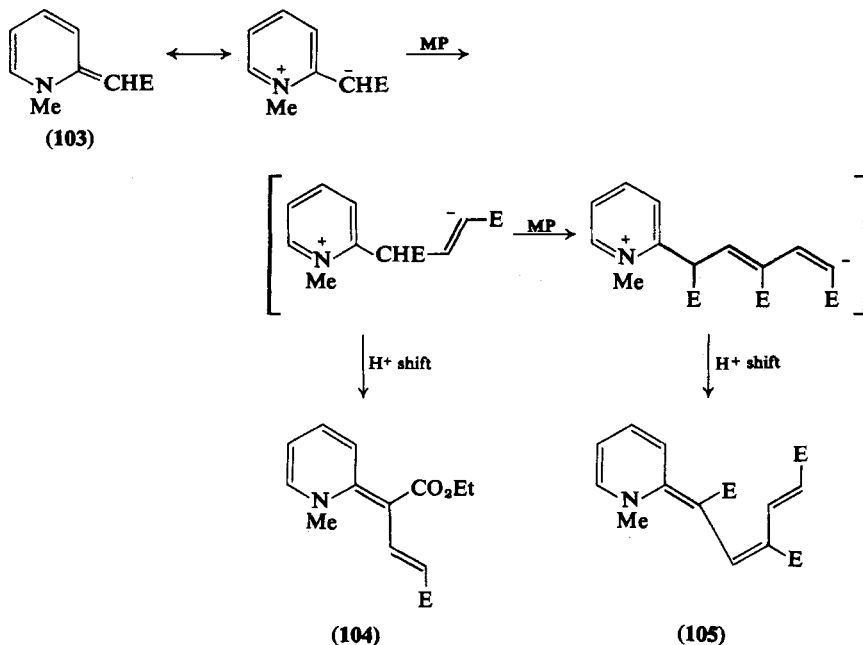
Methyl groups attached to the pyridine ring are not usually involved in reactions with MP, but a minor product from 4-methylpyridine is the dihydropyridine **102**.²⁹¹ It could be formed via a zwitterion corresponding to **95**, proton transfer giving **101**, addition to another molecule of MP, and a further proton shift.



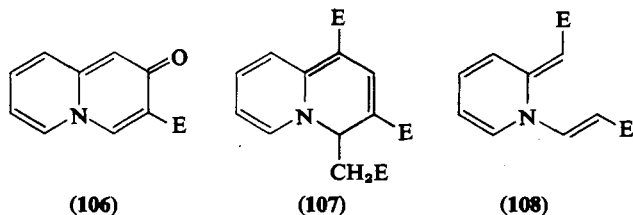
²⁹³ V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.* **83**, 458 (1961).

²⁹⁴ V. Boekelheide and T. Small, *J. Am. Chem. Soc.* **83**, 462 (1961).

Dihydropyridines, such as **103**, obtained from the corresponding pyridinium salts with bases, usually give 1:2 molar adducts (e.g., **105**) with MP, but-1-yn-3-one, and 3-phenylprop-1-yn-3-one. Occasionally 1:1-molar adducts such as **104** can be isolated, and it is noteworthy that the acetylenes appear to attack only the exocyclic double bond.²⁹⁵

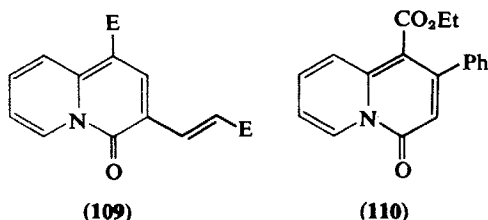


Methyl 2-pyridylacetate in ether with MP yields a mixture of **106**, **107**, and **108** which could be formed through a zwitterion corresponding to **95**,²⁹⁶ and **109**. The 1-propanoyl derivative of **109** is obtained from 1-(2-pyridyl)butan-2-one. However, ethyl 2-pyridylacetate with phenylpropionic esters apparently gave only **110**, and, if sodium methoxide was



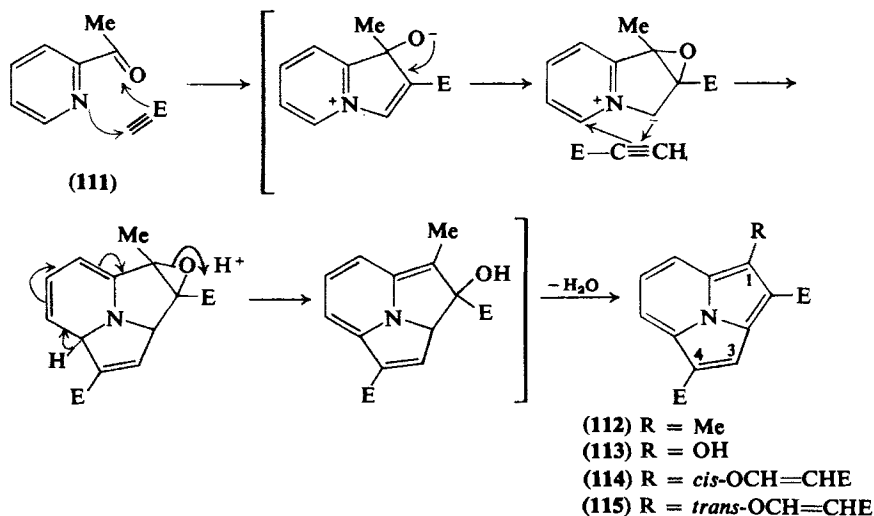
²⁹⁵ R. M. Acheson and J. M. Woollard, *J. Chem. Soc., Perkin Trans. I*, 744 (1975).

²⁹⁶ R. M. Acheson and J. M. Woollard, *J. Chem. Soc., Perkin Trans. I*, 740 (1975).



employed as a catalyst, ester exchange giving the corresponding methyl ester took place.^{297,298}

Refluxing 2-acetylpyridine (**111**) with MP gives a remarkable 29% yield of pyrrolo[2,1,5-*cd*]indolizine (**112**), which may be formed by the route (Scheme 5) outlined.²⁹⁶ Ethyl pyridine-2-carboxylate, presumably by a similar mechanism, yields a mixture of three pyrrolo[2,1,5-*cd*]-indolizines (**113**, **114**, and **115**).²⁹⁶



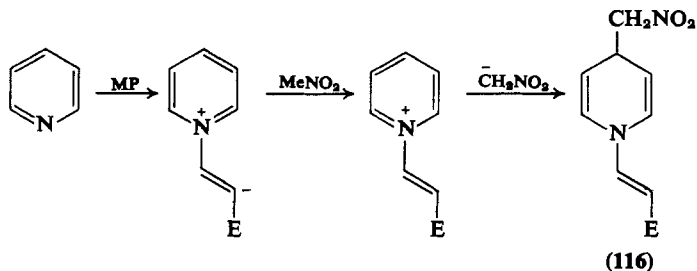
SCHEME 5

Pyridine and its 3-methyl and 3,5-dimethyl derivatives, with 1 mole of MP and a compound with an activated methylene group yield the corresponding 1,4-dihydropyridines (e.g., **116**). But-1-yn-3-one behaves like MP in most of these reactions at -20° , but tars are obtained at 0° .²⁹⁹ Active methylene compounds successfully employed include

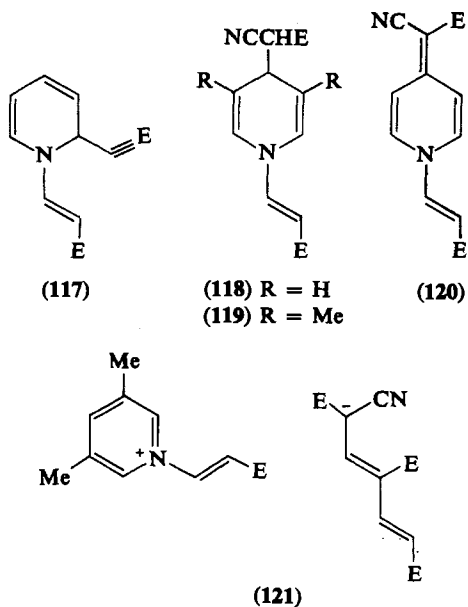
²⁹⁷ H. N. Al-Jallo and F. H. Al-Hajjar, *J. Chem. Soc. C*, 2056 (1970).

²⁹⁸ Y. Masaki, H. Otsuka, Y. Nakayama, and M. Hioki, *Chem. Pharm. Bull.* **21**, 2780 (1973).

²⁹⁹ R. M. Acheson and J. M. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 446 (1975).



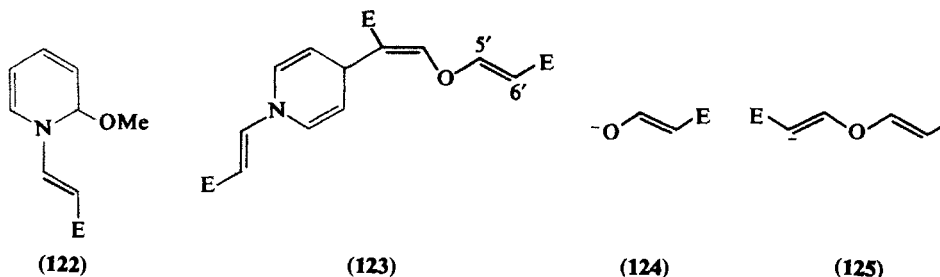
nitroethane and nitromethane, pentane-2,4-dione, 3-methylpentane-2,4-dione, methyl cyanoacetate and acetoacetate, and malononitrile.³⁰⁰ The products were invariably 1,4-dihydropyridines, and some **117** was always obtained when nitromethane provided the carbanion; this carbanion must compete with that obtainable from MP through loss of the acetylenic proton. No adducts involving acetone, acetophenone, or diethyl malonate could be detected in these reactions, possibly due to the preferential attack of the less sterically demanding or more easily formed carbanion from MP. From the reaction with methyl cyanoacetate, the expected adduct (**118**) and its dehydrogenation product (**120**) were obtained, oxidation having occurred *in situ*; occasionally



³⁰⁰ R. M. Acheson and J. M. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 438 (1975).

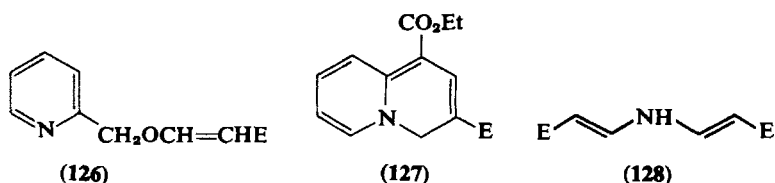
only the oxidized compound is isolable. These adducts must be able to dissociate into the pyridinium salts and the appropriate anions, for heating **119** with nitromethane gave the 3,5-dimethyl derivative of **116**.³⁰⁰ On one occasion 3,5-dimethylpyridine with methyl cyanoacetate and MP yielded the purple salt **121**³⁰⁰; a similar compound has been obtained using DMAD.³⁰¹

In rather unreliable reactions, pyridine and its 3-methyl and 3,5-dimethyl derivatives with MP and 1 mole of methanol yield 2-methoxy-1,2-dihydropyridines (e.g., **122**).²⁹² This contrasts with DMAD which yields indolizines (e.g., **35** and **36**), perhaps because the extra ester group encourages the methoxide ion to add to the exocyclic double bond, but 4-methylpyridine with MP gives the same products (see earlier) as obtained in the absence of added methanol.²⁹² Replacing the methanol by water gave compounds exemplified by **123**, where the 5',6'-double



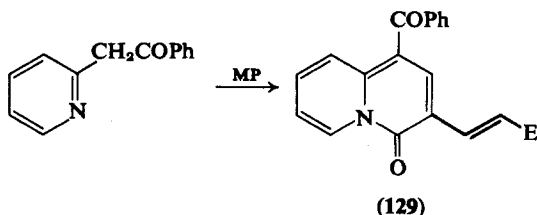
bond is cis or trans. These compounds could be formed by abstraction of a proton from the water by the zwitterion **95**, addition of the resulting hydroxyl to MP, and proton transfer to give **124**. This anion can then add to another molecule of MP to yield **125**, which combines with the pyridinium cation.²⁹²

2-Pyridylmethanol reacts only at the hydroxyl group with MP to give a mixture of the geometrical isomers of **126**,²⁹² ethyl 2-pyridylacrylate yields the 4*H*-quinolizine (**127**; cf. **33**),²⁹² whereas the only isolable product from 4-imino-1-methyl-1,4-dihydropyridine is **128**.²⁹⁵ 2-Phenacylpyridine with MP in acetonitrile yields the 4-quinolizone **129**, where



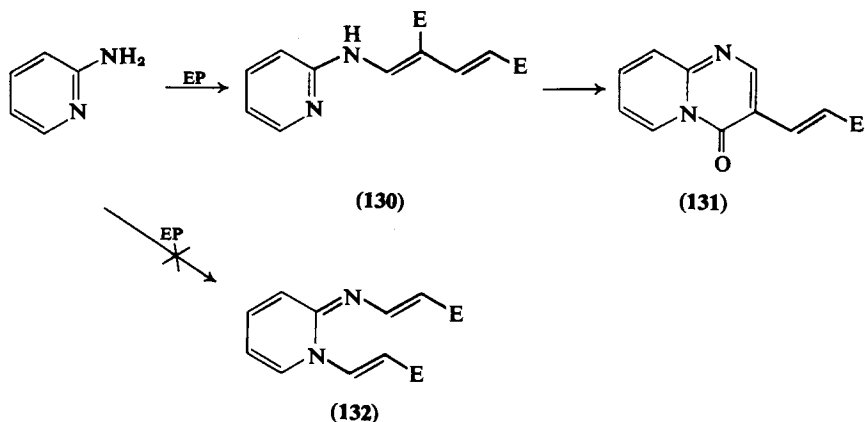
³⁰¹ P. Bamfield, A. Crabtree, and A. W. Johnson, *J. Chem. Soc.*, 4355 (1965).

nucleophilic attack on the acetylene must originate from the activated methylene group.³⁰²



7. Aminopyridines and Derivatives

The addition of propiolic esters to substituted 2-aminopyridines has been examined by three groups.³⁰³⁻³⁰⁵ The most recent study³⁰⁵ is definitive. The 1:2 molar adduct was first³⁰³ thought to be **132** but is, in fact,³⁰⁵ **130**, which cyclizes to **131**. In two cases,³⁰⁵ compounds with structure **132** were obtained, and the NMR spectra for all these adducts were compared.



Addition of DMAD to 2-hydrazinopyridine gave the hydroxypyrazole **134**.^{306,307} In a further study of this reaction, Le Count and Greer³⁰⁸ obtained the succinate **133** and cyclized it with acetic anhydride to **135**.

³⁰² R. M. Acheson and J. N. Bridson, *J. Chem. Soc. C*, 1143 (1969).

³⁰³ G. R. Lappin, *J. Org. Chem.* **26**, 2350 (1961).

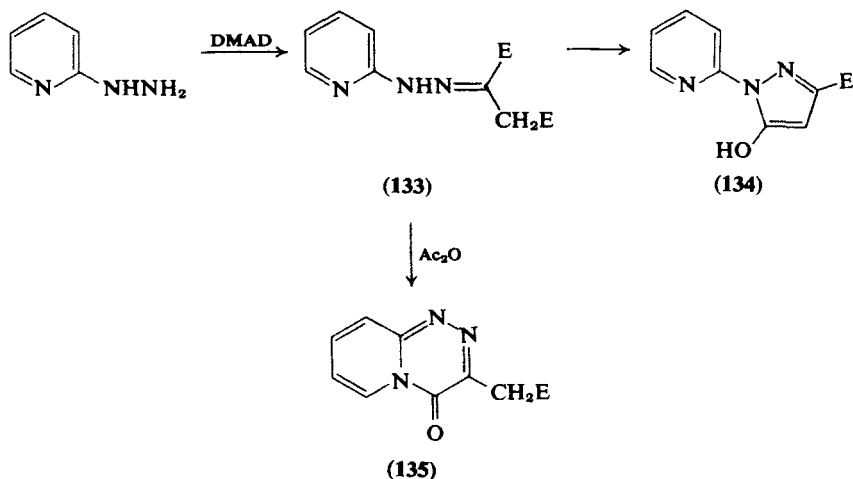
³⁰⁴ I. J. Pachter, *J. Org. Chem.* **26**, 4157 (1961).

³⁰⁵ J. G. Wilson and W. Bottomley, *J. Heterocycl. Chem.* **4**, 360 (1967).

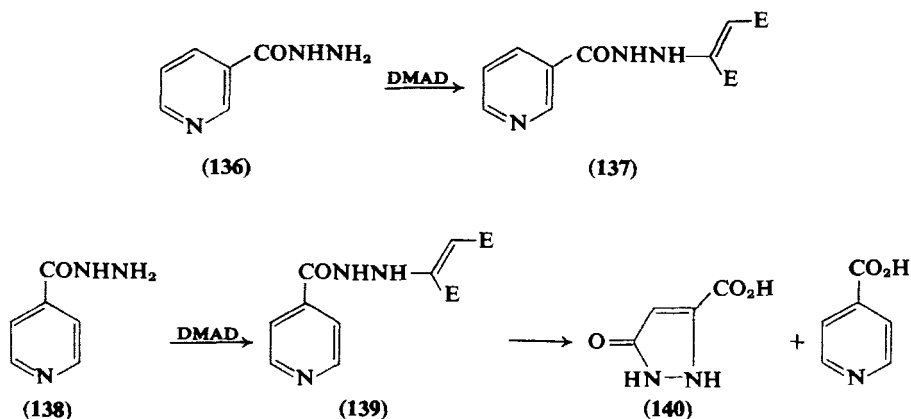
³⁰⁶ M. Brugger, H. Wamhoff, and F. Korte, *Annalen* **757**, 100 (1972).

³⁰⁷ M. D. Nair, *Indian J. Chem.* **9**, 104 (1971).

³⁰⁸ D. J. Le Count and A. T. Greer, *J. Chem. Soc., Perkin Trans. 1*, 297 (1974).

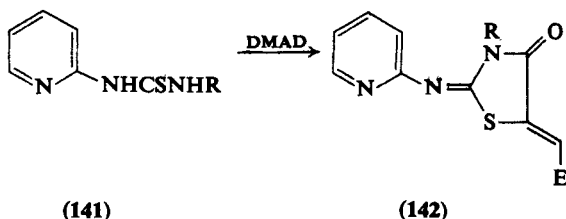


The addition of DMAD to nicotinic (136) and isonicotinic (138) acid hydrazides takes place in the expected Michael fashion, giving 137 and 139. The isonicotinic adduct on treatment with acid gave the pyrazolone carboxylic acid 140.³⁰⁹ Pyridylthioureas (141) add DMAD to give 142.³¹⁰



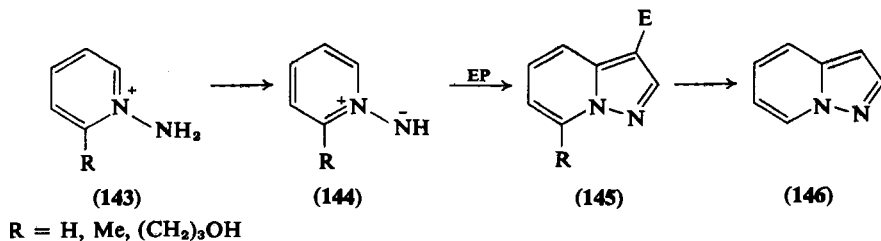
³⁰⁹ G. Caronna and S. Palazzo, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* 30, 31 (1969–1970) [*CA* 77, 151,835 (1972)].

³¹⁰ B. Stanovnik and M. Tisler, *Monatsh.* 104, 1034 (1973).

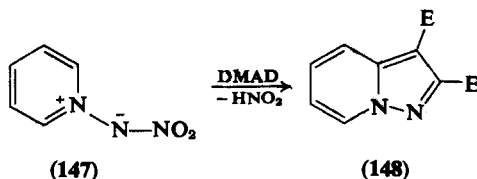


8. Nitrogen Ylids of Pyridine and Acetylenic Esters

When a solution of 1-aminopyridinium iodide (**143**) in DMF was treated with anhydrous potassium carbonate, the mixture developed the deep blue color characteristic of pyridine 1-imine (**144**); addition of EP caused an immediate exothermic reaction giving the pyrazolopyridine **145** in 48% yield³¹¹; hydrolysis and decarboxylation gave a high yield of pyrazolo[1,5-*a*]pyridine (**146**).³¹¹ Many reactions of this type have now been carried out,³¹² and the regioselectivity for the cyclization of 3-substituted derivatives has been examined.³¹³



A new variation is the treatment of **147** with DMAD, in which case **148** is formed.³¹⁴



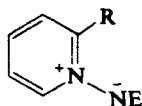
³¹¹ V. Boeckelheide and N. A. Fedoruk, *J. Org. Chem.* **33**, 2062 (1968).

³¹² R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962).

³¹³ Y. Tamura, Y. Sumida, Y. Miki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 406 (1975).

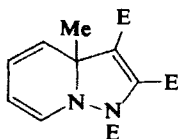
³¹⁴ J. Arriau, J. Deschamps, J. R. C. Duke, J. Epszajn, A. R. Katritzky, E. Lunt, J. W. Mitchell, S. Q. A. Rizvi, and G. Roch, *Tetrahedron Lett.*, 3865 (1974).

Sasaki *et al.*³¹⁵ have studied reactions of DMAD with many 1-alkoxy-carbonyliminopyridinium ylids (**149**) under a variety of conditions, and only the main observations can be discussed here. Without ring substituents or alkyl substituents at positions 3, very poor yields of the

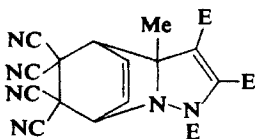


(149) R = H

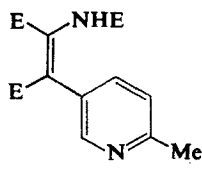
(150) R = Me



(151)

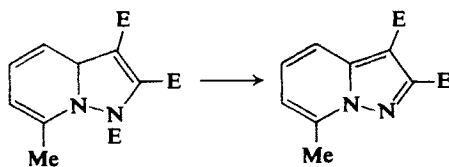


(152)



(153)

azaindolizines (pyrazolo[1,5-*a*]pyridines) (**148**) were obtained, and the yields increased to ca. 28% for the 4-methyl derivatives. The presence of tetracyanoethylene (TCNE) as a dehydrogenating agent made little difference. The 2-methyl derivative (**150**) with DMAD underwent cycloaddition in both possible modes to give **151** and **154**. In the absence of TCNE, compound **151** was isolable and, on subsequent treatment with TCNE, it gave the Diels-Alder adduct **152** in 70% yield. However **151** was unstable and on standing for 3 days at room temperature was converted into the pyridine **153**. If TCNE was added to the reacting



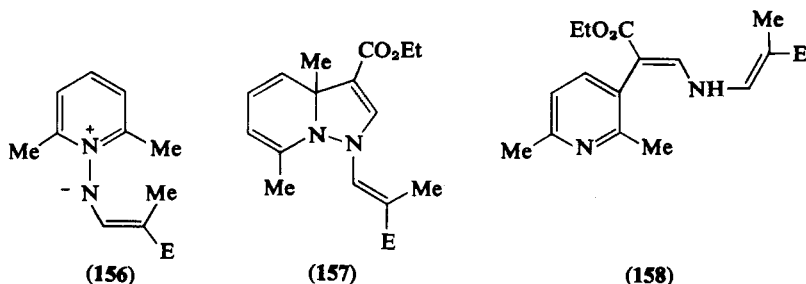
(154)

(155)

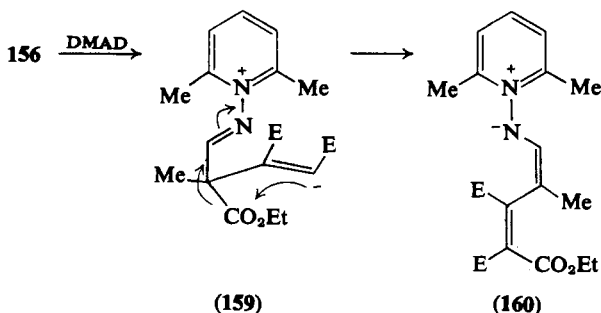
mixture of the ylid and DMAD as soon as the blue color of the *N*-imide had disappeared, then the azaindolizine **155** was obtained as well as **152**. The alternative cyclization to **154** had, therefore, taken place. In the one instance examined EP behaved analogously to DMAD.

³¹⁵ T. Sasaki, K. Kanematsu, and K. Kakehi, *J. Org. Chem.* **36**, 2978 (1971).

N-(Vinylimino)pyridines (e.g., **156**) with EP add initially in the expected fashion to give intermediates (**157**) which rearrange to give the products isolated (**158**)³¹⁶ in a similar way that **151** isomerizes to **153**.



Migratory aptitudes in this type of reaction between 1-benzoylimino-pyridines with DMAD have also been studied.³¹⁷ Treating **156** with DMAD gave a new ylid (**160**), an ester shift³¹⁸ having occurred; no compound corresponding to **157** was formed.³¹⁶



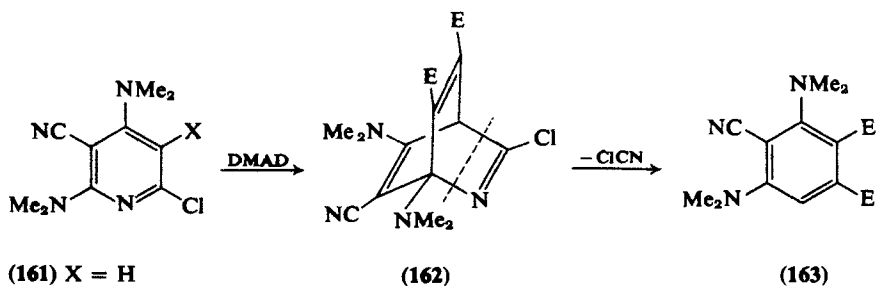
9. Miscellaneous Pyridines with Acetylenic Esters

The first addition of a fully aromatic pyridine, as opposed to a 2-pyridone, across the 2,5-positions, which might be a concerted Diels-Alder reaction, takes place between the bis-dimethylaminopyridine (**161**) and DMAD at 110°. The product (**163**) was obtained in 67% yield and appears to be formed via **162**, which undergoes a retro-Diels-

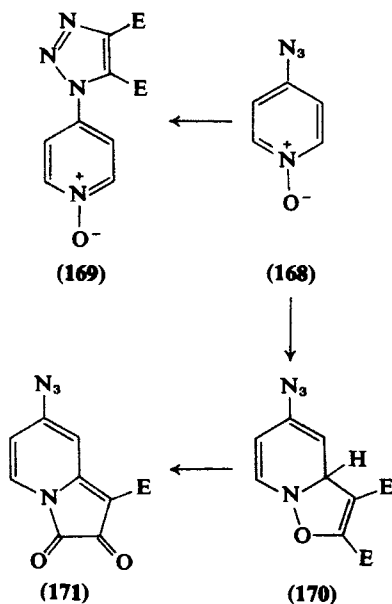
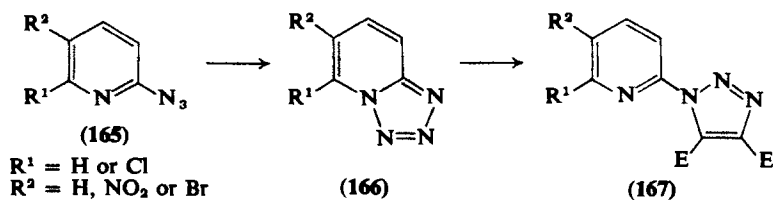
³¹⁶ T. Sasaki, K. Kanematsu, and K. Kakehi, *Tetrahedron Lett.*, 5245 (1972).

³¹⁷ T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Jpn.* **45**, 2050 (1972) [*CA* **77**, 114,196 (1972)].

³¹⁸ R. M. Acheson, *Acc. Chem. Res.* **4**, 177 (1971).



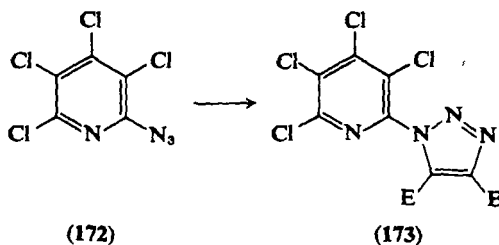
Alder reaction.³¹⁹ With EP and aluminum chloride³²⁰ in chloroform, compound **161** gave mainly **164**,³¹⁹ due to the electrophilic attack on the enaminic-type electron-rich 3-position of this particular pyridine.



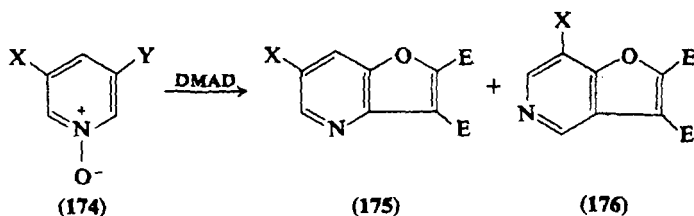
³¹⁹ T. Sasaki and A. Kojima, *Tetrahedron Lett.*, 4593 (1971).

³²⁰ P. Yates and P. Eaton, *J. Am. Chem. Soc.* **82**, 4436 (1960).

2-Azidopyridines (165) exist as the tetrazoles 166, but with DMAD they give the adducts 167.³²¹ 4-Azidopyridine 1-oxide (168) adds DMAD to give 169, but in methanol the reaction takes a different course giving 171, possibly by way of 170.³²¹



Abramovitch, Challand, and Yamada³²² added thermally DMAD to 2-azido-3,4,5,6-tetrachloropyridine (172) and obtained 85% of the 1,2,3-triazole derivative (173), with no evidence for the generation of the nitrene. A one-step furopyridine synthesis of a mixture of 175 and 176 is achieved by treating the 1-oxide 174 with DMAD in hot toluene, rearrangements having taken place.³²³



B. PYRIDAZINES

1. Pyridazine and Alkyl- and Arylpyridazines

Pyridazine with DMAD in methanol³²⁴ yield the azaindolizine 177, whereas in acetonitrile the 4*H*-azaquinolizine (179)³²⁵ is formed. In methanol, 3-methylpyridazine gives³²⁴ the methyl analog 178, but in

³²¹ T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron* **27**, 5121 (1971).

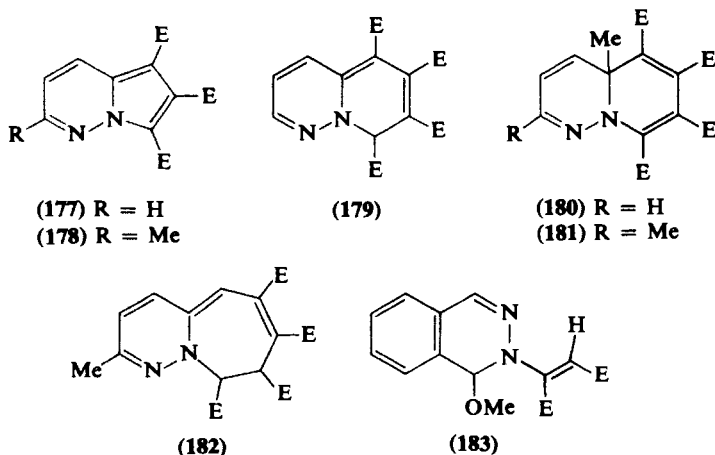
³²² R. A. Abramovitch, S. R. Challand, and Y. Yamada, *J. Org. Chem.* **40**, 1541 (1975).

³²³ R. A. Abramovitch and I. Shiakai, *J. Am. Chem. Soc.* **97**, 3227 (1975).

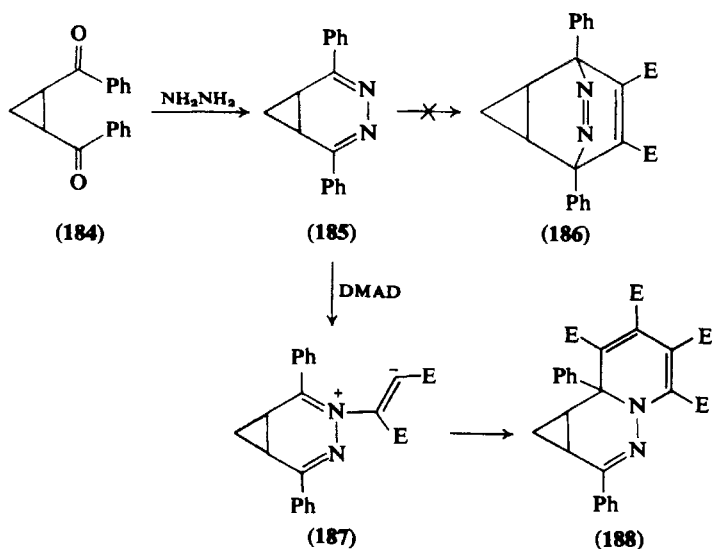
³²⁴ R. L. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 764 (1956).

³²⁵ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 2218 (1968).

acetonitrile,³²⁵ in contrast to the behavior of the unsubstituted hetero-cycle, it forms mainly the bridgehead adduct **180**. In acetonitrile, 3,6-dimethylpyridazine forms the azepine **182** along with a trace of the isomeric quinolizine **181**.³²⁵



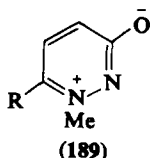
Treatment of dibenzoylcyclopropane (**184**) with hydrazine gave the dihydropyridazine (**185**) which, on treatment with DMAD, showed no tendency to add in a Diels–Alder manner giving **186** but added the ester Michael fashion, giving **188** via **187**.³²⁶



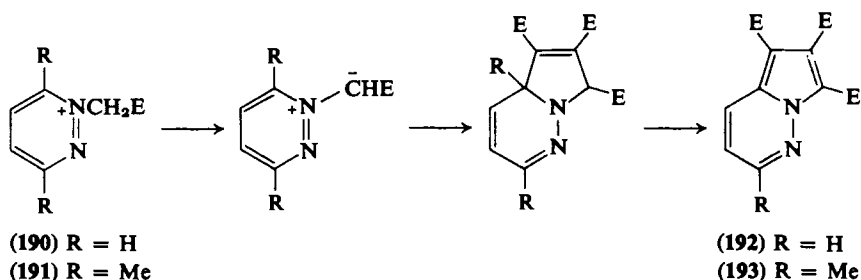
³²⁶ G. Maier and U. Heep, *Chem. Ber.* **101**, 1371 (1968).

2. Pyridazine Ylids

Pyridazine betaines (**189**) do not appear to react with activated acetylenes.³²⁷ Pyridazine ylids, prepared *in situ* from salts such as **190**,



often with triethylamine in dichloromethane, with DMAD give pyrrolo-[1,2-*b*]pyrazines (e.g., **192**), aromatization having taken place. An attempt to block the aromatization by using **191** failed, a methyl group being eliminated, and the product (**193**) was identical with that obtained from 3-methylpyridazine and DMAD in methanol.³²⁸



Many pyridazinium ylids have been employed³²⁹⁻³³² in similar reactions with DMAD and EP. In the case of **194** the intermediate compound **195** was obtained³³⁰ and lost hydrogen cyanide to give the end product **196**. If a methoxyl group was present at a position that could prevent cyclization, then it was eliminated; for example, **197** gave only **198**.³²⁹ A systematic study of the effect of substituents attached to the negative carbon atom of the ylid (cf. **194**) has been made³³³: the least stable ylids gave the poorest yields of pyrrolopyrazines.

³²⁷ N. Dennis, A. R. Katritzky, and M. Ramaiah, *J. Chem. Soc., Perkin Trans. I*, 1506 (1975).

³²⁸ R. L. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 764 (1956).

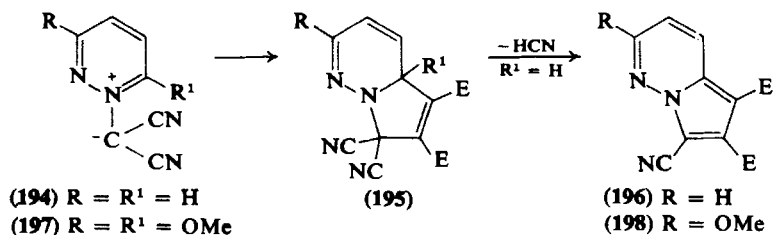
³²⁹ T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.* **36**, 813 (1971).

³³⁰ Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* **19**, 2106 (1971).

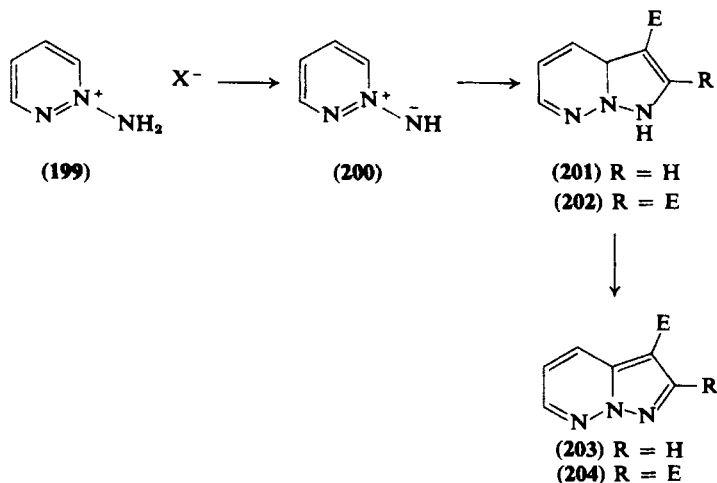
³³¹ D. G. Farnum, R. G. Alaimo, and J. M. Dunston, *J. Org. Chem.* **32**, 1130 (1967).

³³² M. Petrovanu, E. Stefanescu, and I. Druta, *Rev. Roum. Chim.* **16**, 1107 (1971).

³³³ Y. Masaki, H. Otsuka, Y. Nakayama, and M. Hioki, *Chem. Pharm. Bull.* **21**, 2780 (1973).



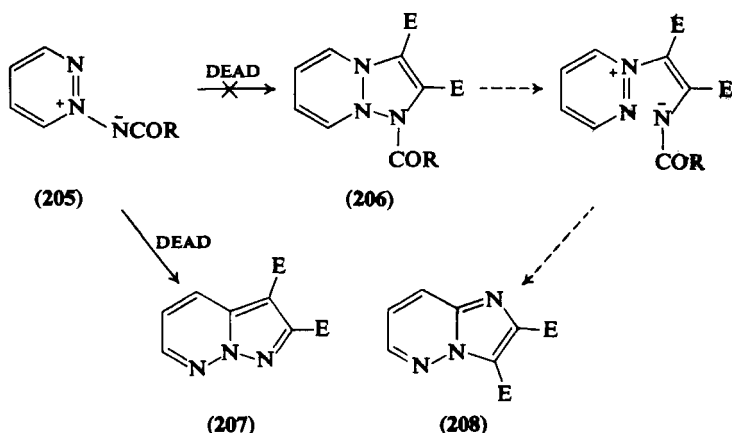
1-Aminopyrazinium salts (199) with potassium carbonate give the 1-imides (200), which are readily converted into the corresponding pyrazolo[1,5-*b*]pyrazine (e.g., 204) by DMAD, DEAD, or EP (e.g., 203).^{330,334} No products corresponding to 201 were detected, aromatiza-



tion being too rapid. *N*-Acyl derivatives (205) of 200 were also treated with DMAD and gave pyrazolopyridazines (e.g., 204) but more slowly, perhaps because the negative charge is resonance-stabilized.³³⁴ No evidence was found that these *N*-imides (205) could behave as azimines and in consequence cyclize onto nitrogen to give structures such as 206.³³⁴ This last would be expected to rearrange to 208, which was made independently and could not be detected in the reaction product (207).^{334,335}

³³⁴ C. W. Rees, R. W. Stephenson, and R. C. Storr, *Chem. Commun.*, 941 (1974).

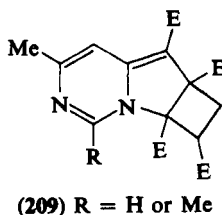
³³⁵ K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* 22, 1814 (1974).



C. PYRIMIDINES

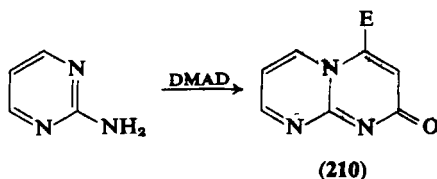
1. Alkylpyrimidines

Little work has been done with simple pyrimidines. 4,6-Dimethyl- and 2,4,6-trimethylpyrimidine in acetonitrile with DMAD gave low yields of 1:2 molar adducts, originally considered³³⁶ to be pyrimido[1,2-*a*]-azepines, but which are almost certainly cyclobuta[4,5]pyrrolo[1,2-*c*]-pyrimidines (209).³³⁷



2. Functionally Substituted Pyrimidines

2-Aminopyrimidine adds DMAD in methanol at 0° to give 210.³³⁸

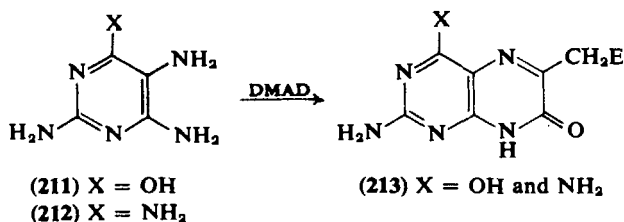


³³⁶ R. M. Acheson, M. W. Foxton, and J. K. Stubbs, *J. Chem. Soc. C*, 926 (1968).

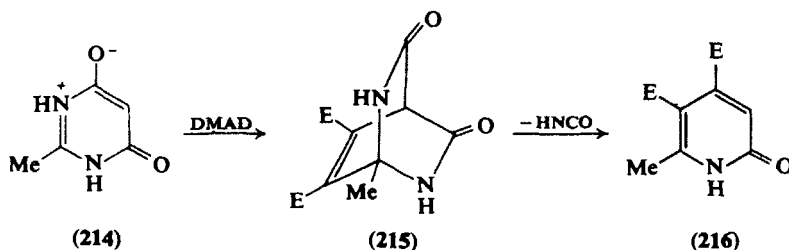
³³⁷ R. M. Acheson, G. Procter, and S. R. Critchley, *Chem. Commun.*, 962 (1976); R. M. Acheson and G. Procter, *J. Chem. Soc., Perkin Trans. 1*, 1924 (1977).

³³⁸ M. N. Sharma, *Curr. Sci.* 43, 179 (1974) [*CA* 81, 3891 (1974)].

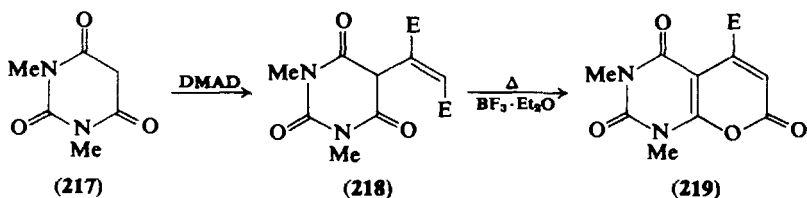
2,5,6-Triamino-4-pyrimidone (**211**) and 2,4,5,6-tetraminopyrimidine (**212**) add DMAD and DEAD to give the isoxanthopterin-6-acetates and their 4-amino analogs (**213**)³³⁹ via Michael reactions starting with the most basic (5-)amino groups.



2-Methyl-4,6-pyrimidinedione (**214**) adds DMAD to give the pyridone **216** via the unstable bicyclic adduct (**215**).³⁴⁰



With triethylamine in methanol, 1,3-dimethylbarbituric acid (**217**) adds DMAD in Michael fashion to give **218**, which, after heating to 170° or treatment with boron trifluoride etherate at 120° to 130° gave pyrano[2,3-*d*]pyrimidine (**219**).³⁴¹



Reaction of various 6-alkylaminouracils (**220**) with DMAD in DMF gave 5-substituted products (**222**).³⁴² This is a remarkable reaction, for

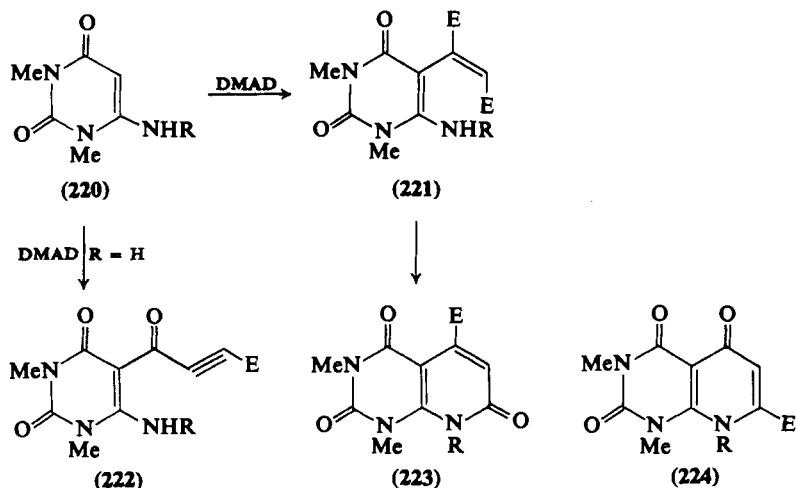
³³⁹ Y. Iwanami, *Bull. Chem. Soc. Jpn.* **44**, 1314 (1971).

³⁴⁰ A. E. A. Porter and P. G. Sammes, *Chem. Commun.*, 1103 (1970).

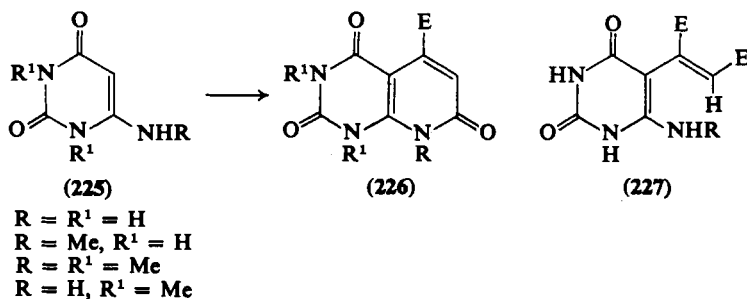
³⁴¹ A. Subba Rao and R. B. Mitra, *Indian J. Chem.* **12**, 1028 (1974) [*CA* **82**, 112023 (1975)].

³⁴² J. L. Shim, R. Niess, and A. D. Broom, *J. Org. Chem.* **37**, 578 (1972).

DMAD reacts almost invariably with nucleophiles at the triple bond and not at a carbonyl group. Ogura and Sakaguchi³⁴³ reacted 6-amino- and 6-(substituted amino)-1,3-dimethyluracils (**220**; R = H, Me, Ph, PhCH₂) with DMAD in methanol and obtained a mixture of 5-oxo- (**224**) and 7-oxopyrido[2,3-*d*]pyrimidines (**223**), together with the open-chain intermediate (**221**), which was cyclized to **223** by heating in DMF.



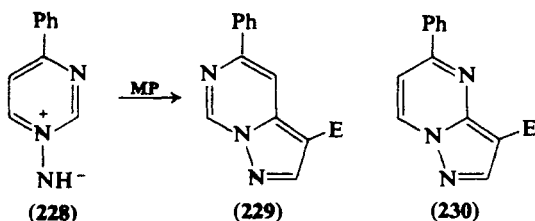
This work has been further developed using the uracils **225** which give **226**.³⁴⁴ A 6-methylamino group exerts a profound influence on the course of the reaction with DMAD in aprotic solvents to give C₅ alkylation or acylation; in protic media only products of C₅ alkylation



³⁴³ H. Ogura and M. Sakaguchi, *Chem. Pharm. Bull.* **21**, 2014 (1973).

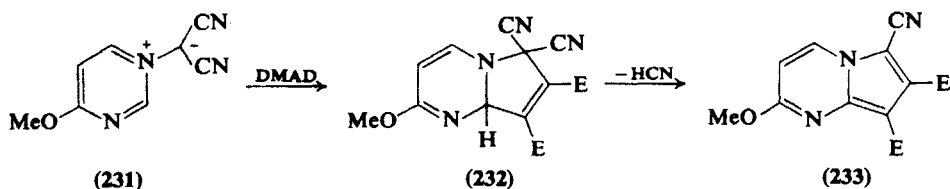
³⁴⁴ A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.* **41**, 1095 (1976).

were obtained. In aprotic solvents, the maleate (**227**) was obtained from **225** ($R = R^1 = H$) and DMAD, whereas the corresponding fumarate was obtained in methanol.

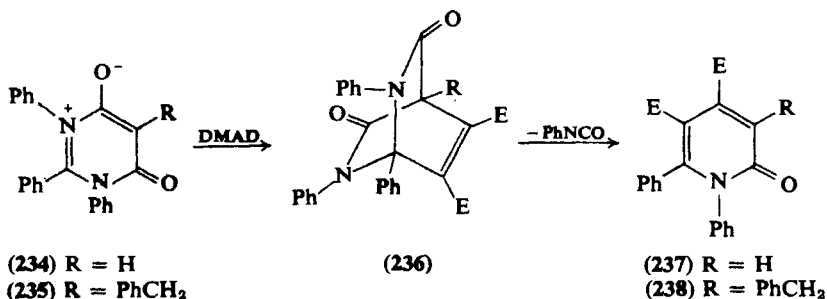


Treatment of the pyrimidinimines **228** with propiolic ester gave **229**.³⁴⁵ The authors state that **230** was expected because of the lower electron density at C-2, but spectroscopic data provided convincing evidence for the alternative structure.

Pyrimidinium methylide (**231**) added DMAD³³⁰ to give **233**, presumably via **232**, which was not isolated.



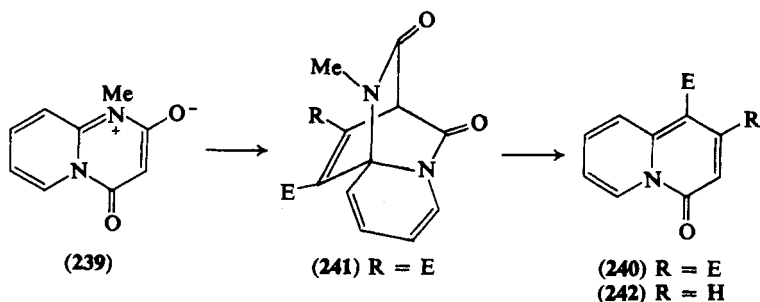
Cycloadditions to mesomeric pyrimidine betaines (**234** and **235**) with DMAD in refluxing chlorobenzene gave high yields of the pyridones **237** and **238** via the intermediate cycloadducts **236**, which were not



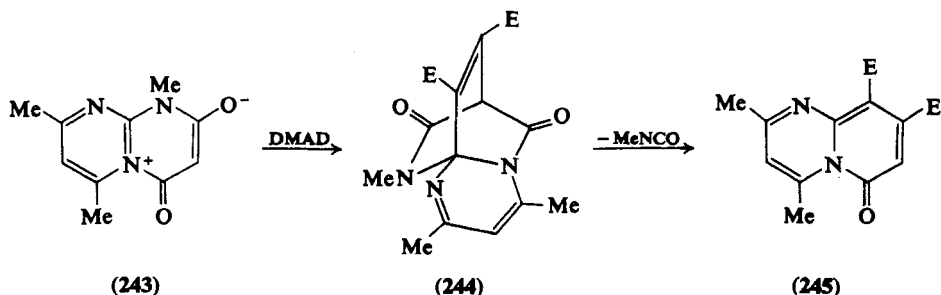
³⁴⁵ K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 1814 (1974) [*CA* **81**, 136,104 (1974)].

isolated.^{346,347} Propiolic ester did not form well-defined products with these substrates.

Potts and Sorm³⁴⁸ studied the 1,4-cycloaddition of anhydro-2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyridinium hydroxide (**239**) which gave 64% of the quinolizin-4-one (**240**) after refluxing for 24 hours in xylene with DMAD, via the postulated intermediate **241**. Methyl propiolate formed **242**.



The mesoionic pyrimidine **243**³⁴⁹ (from carbon suboxide and 4,6-dimethyl-2-methylaminopyrimidine) added DMAD (and dicyanoacetylene and 1,3-diphenyl-1-oxoprop-2-yne) in boiling xylene giving a good yield of the pyrido[1,2-*a*]pyrimidin-6-one (**245**). Phenylpropionic ester and EP merely converted **243** back into 4,6-dimethyl-2-methylaminopyrimidine. The fused pyrimidine **247**, obtained from benzimidazole (**246**)



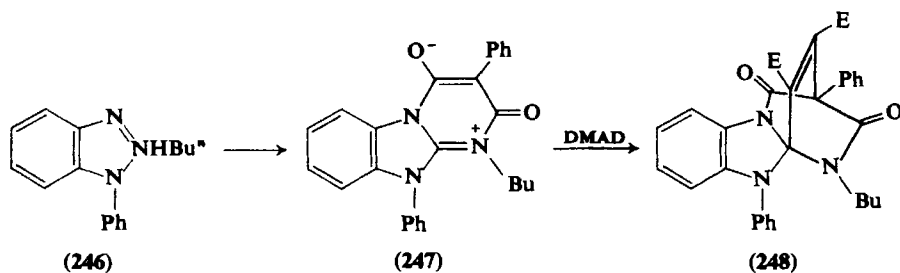
³⁴⁶ T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.* 10, 925 (1971).

³⁴⁷ K. T. Potts and M. Sorm, *J. Org. Chem.* 37, 1422 (1972).

³⁴⁸ K. T. Potts and M. Sorm, *J. Org. Chem.* 36, 8 (1971).

³⁴⁹ K. T. Potts and R. C. Hsia, *J. Org. Chem.* 38, 3485 (1973).

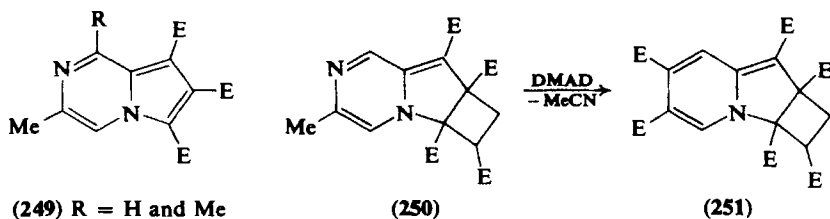
and phenylmalonic ester, added DMAD to give the stable adduct **248**.³⁵⁰



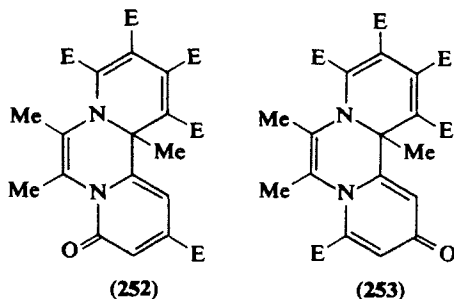
D. PYRAZINES

1. Alkylpyrazines

2-Methyl- and 2,6-dimethylpyrazines with DMAD in acetonitrile yield the corresponding azaindolizines (**249**),³⁵¹ whereas 2,5-dimethylpyrazine gives a 1:3-molar adduct less the elements of acetonitrile. This adduct, originally described as an azepine,³³⁶ is probably the cyclobutaindolizine **251**,³³⁷ and could be formed via **250** by cycloaddition of DMAD across the dihydropyrazine ring and elimination of acetonitrile.



2,3,5,6-Tetramethylpyrazine combines with 3 moles of DMAD and loses methanol, giving product **252** or the isomer **253**.³³⁶

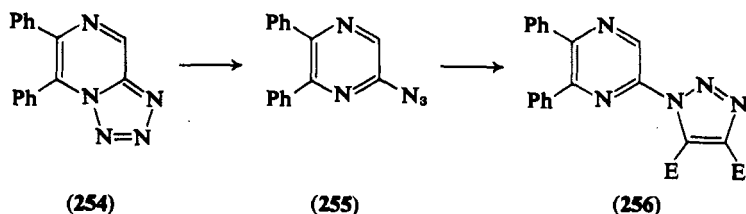


³⁵⁰ N. F. Elmore, unpublished observation.

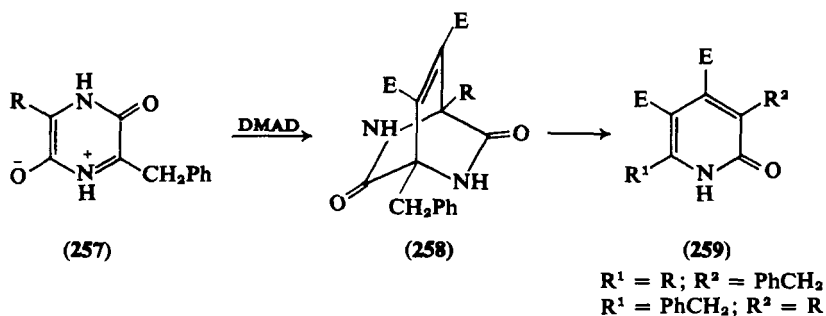
³⁵¹ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 2218 (1966).

2. Other Functionally Substituted Pyrazines

The azidopyrazine (**255**) in equilibrium with the tetrazole **254**, adds DMAD in chloroform giving **256** (15%).³⁵²

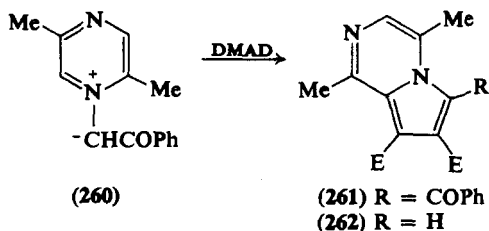


Sammes *et al.*³⁵³ added DMAD to the pyrazine-2,5-dione **257** ($R = \text{Me}$) at room temperature in DMF and isolated the primary cycloadduct **258**, which, on heating for 15 minutes in DMF at 100° , gave equal amounts of the two possible pyridones **259**. The dibenzyl compound (**257**; $R = \text{CH}_2\text{Ph}$) behaved similarly.



3. Pyrazine Ylids

The phenacyl ylid (**260**) from 2,5-dimethylpyrazine with DMAD in the presence of palladium on charcoal gave two products (**261**, **262**).³⁵⁴

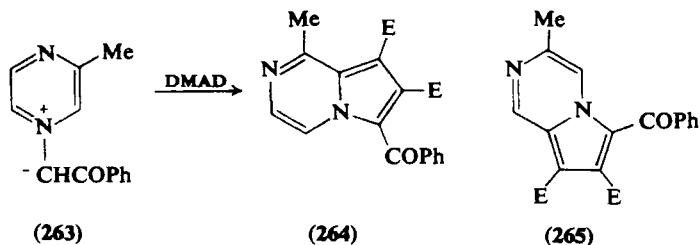


³⁵² T. Sasaki, K. Kanematsu, and M. Murata, *J. Org. Chem.* **36**, 446 (1971).

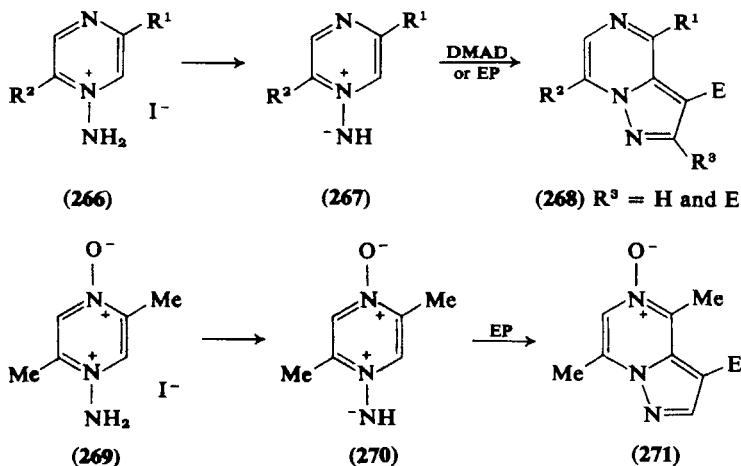
³⁵³ P. J. Machin, A. E. A. Porter, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 404 (1973).

³⁵⁴ V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.* **83**, 458 (1961).

The corresponding ylid from 2-methylpyrazine with DMAD in acetonitrile gave 4% of **264**, and in refluxing chloroform, 8.5% of a 2:1 mixture (NMR) of adducts that were stated to be **264** and **265** on the presumption that the initial ylid was a single substance (**263**).³²⁹



The syntheses of some pyrazolo[1,5-*a*]pyrazines from *N*-aminopyrazinium derivatives have been described.³⁴⁵ Treatment of **266** ($\text{R}^1, \text{R}^2 = \text{H}$ or Me) with base gave **267**, which cyclized to **268** with EP or DMAD. The *N*-imino derivative (**270**), from the interesting *N*-aminopyrazinium *N'*-oxide salt (**269**) gave 41% of **271** with EP.³⁴⁵



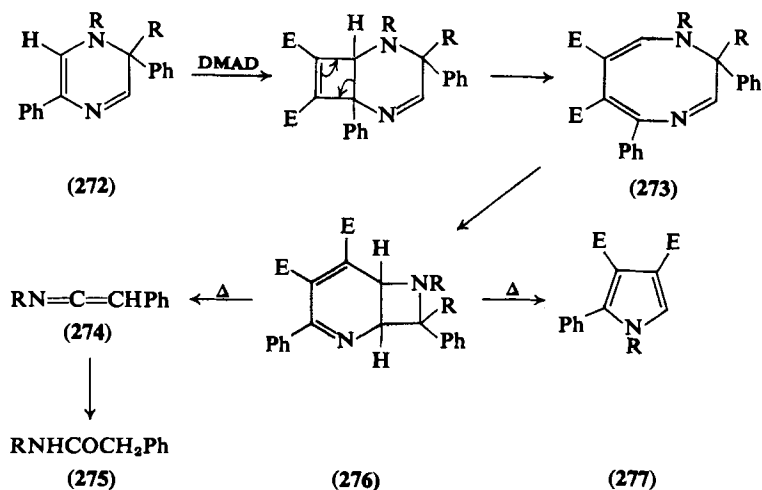
4. Dihydropyrazines

Lown and Akhtar^{355,356} have described the addition of DMAD to the 1,2-dihydropyrazine derivatives (**272**) and implicated 1,4-diazocine **273** to explain the formation of product **276**. Heating the last briefly in

³⁵⁵ J. W. Lown and M. H. Akhtar, *Tetrahedron Lett.*, 3727 (1973); 179 (1974).

³⁵⁶ J. W. Lown, M. H. Akhtar, and W. M. Dadson, *J. Org. Chem.* **40**, 3363 (1975).

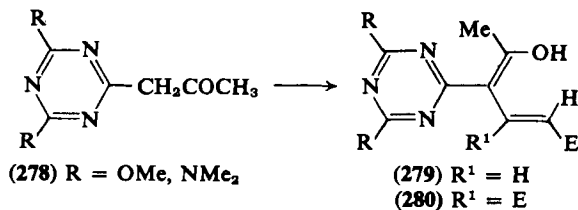
benzene gave the pyrrole **277** and the ketenimine **274** which was hydrolyzed with acid to give the phenylacetamide **275**.



E. 1,3,5-TRIAZINES

1. β -Oxo-s-triazines

Addition of DMAD to some β -oxoalkyl-s-triazines (**278**) leads to **280**,³⁵⁷ and the ease of reaction is dependent on the substituents on the triazine ring. The stereochemistry of the adduct (**279**) from EP is in agreement with the cyclic mechanism leading to a *cis* addition of the dienophile to the enol,³⁵⁸ and bicyclic products were not obtained.

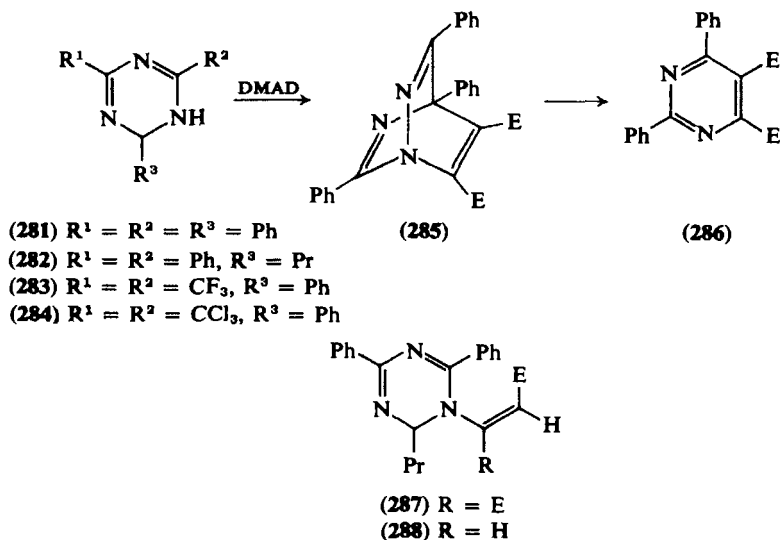


³⁵⁷ Y. Bessière-Chrétien and H. Serne, *J. Heterocycl. Chem.* **11**, 317 (1974).

³⁵⁸ H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **8**, 556 (1969).

2. Dihydro-s-triazines

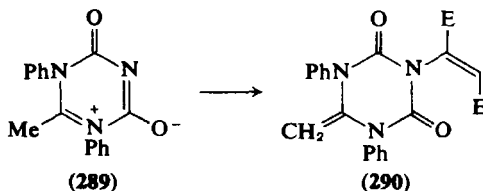
Two Russian papers^{359,360} have described the synthesis and addition of acetylenic esters to dihydro-s-triazines. The triphenyl derivative **281** on heating with DEAD in ether for 3 hours gave 80% of **286**, presumably via **285**. The diphenyl propyl derivative (**282**) added Michael fashion to



the esters to produce **287** and **288**. Triazines **283** and **284** did not react with these acetylenes.

3. Mesomeric s-Triazinium Betaines

Reaction between DMAD and the s-triazine betaines (**289**) in boiling xylene gave only the addition product **290**, no cycloaddition being detected.³⁶¹



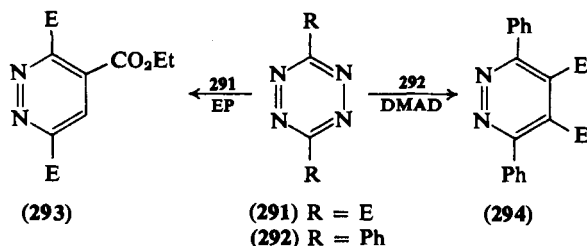
³⁵⁹ V. M. Cherkasov, N. A. Kapran, and V. N. Zavatskii, *Khim. Geterotsikl. Soedin.* **5**, 350 (1969) [*CA* **71**, 30,455 (1969)].

³⁶⁰ V. M. Cherkasov, N. A. Kapran, V. N. Zavatskii, and V. T. Tysba, *Khim. Geterotsikl. Soedin.* **7**, 704 (1971) [*CA* **76**, 126,945 (1972)].

³⁶¹ R. A. Coburn and B. Bhooshan, *J. Heterocycl. Chem.* **12**, 187 (1975).

F. TETRAZINES

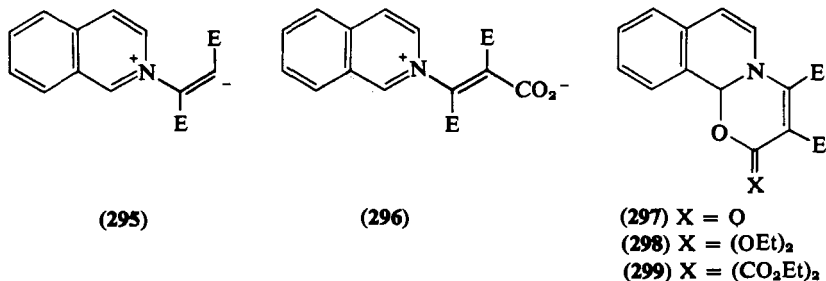
Tetrazines (**291** and **292**) reacted with EP and DMAD to give pyridazines (**293** and **294**) and nitrogen.³⁶² Transformations of **294** have been described.³⁶³



G. QUINOLINES AND ISOQUINOLINES

1. Quinoline and Isoquinoline with DMAD

Quinoline³⁶⁴ and isoquinoline behave much like pyridine toward DMAD, and only the more interesting reactions will be noted. Isoquinoline in ether at -60° with DMAD and carbon dioxide gives, via the postulated intermediate **295**, zwitterion **296** (m.p. 83° – 84°), which is far more stable than its pyridine analogs (cf. **2**).³⁶⁵ Its stereochemistry has not been established but its IR spectrum shows absorption due to the carboxylate anion and excludes the cyclic formulation **297**. Replacing the carbon dioxide by ethyl carbonate gives **298**.³⁶⁶ In wet ether the



³⁶² H. Neunhoeffer and G. Werner, *Annalen*, 437 (1973).

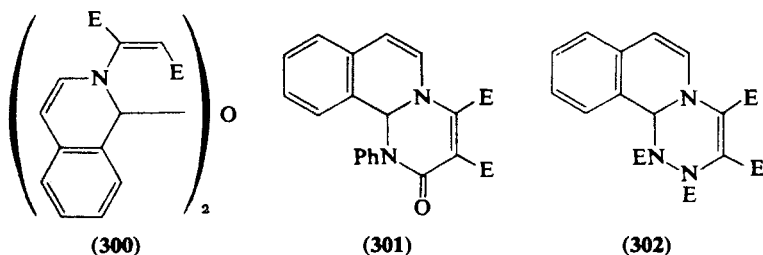
³⁶³ H. Neunhoeffer and G. Werner, *Annalen*, 1955 (1973).

³⁶⁴ R. M. Acheson, N. J. Earl, P. Higham, R. E. Richards, G. A. Taylor, and J. M. Vernon, *Proc. Chem. Soc.*, 281 (1960).

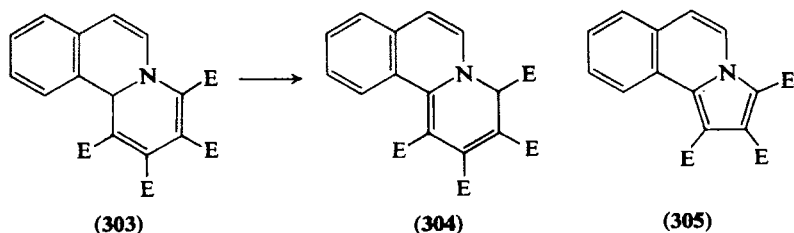
³⁶⁵ R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 2676 (1964).

³⁶⁶ R. Huisgen and K. Herbig, *Annalen* 688, 98 (1965).

product is **300**.³⁶⁵ Intermediate compound **295** has also been trapped by diethyl mesoxalate, phenyl isocyanate, and dimethyl azodiformate which gave **299**, **301**, and **302**, respectively.³⁶⁷ In the absence of carbon



dioxide or other trapping agent, the product is benzoquinolizine (**303**),³⁶⁸ which isomerizes with acid³⁶⁸ or by a [1,5]sigmatropic shift³⁶⁹ to **304**, corresponding to similar reactions in the quinolizine series. The benzo-[e]indolizine (**305**) is obtained when methanol is used as solvent.³⁶⁸



2. 2-Methylquinolines and 1-Methylisoquinolines with DMAD

2-Methylquinoline was treated with DMAD in ether by Diels, Alder, and their collaborators in 1932–1935 and they obtained red, yellow, and colorless adducts.^{370–372} The colorless adduct has not been obtained again. The yellow adduct was identified³⁷³ as 4a-methyl-4aH-benzo[c]-quinolizine (**306**) from its NMR spectrum. The red adduct was first³⁷⁰

³⁶⁷ R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.* **100**, 1094 (1967).

³⁶⁸ R. M. Acheson and F. Hole, *J. Chem. Soc.*, 748 (1962).

³⁶⁹ R. M. Acheson and J. K. Stubbs, *J. Chem. Soc. C*, 3285 (1971).

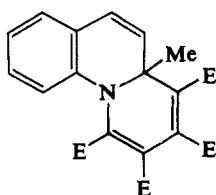
³⁷⁰ O. Diels, K. Alder, T. Kashimoto, W. Friedrichsen, W. Eckhardt, and H. Klare, *Annalen* **498**, 16 (1932).

³⁷¹ O. Diels, K. Alder, W. Friedrichsen, E. Petersen, Brondersen, and H. Kech, *Annalen* **510**, 87 (1934).

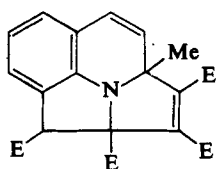
³⁷² O. Diels and H. Kech, *Annalen* **519**, 140 (1935).

³⁷³ E. E. van Tamelen, P. E. Aldrich, P. Bender, and G. R. Miller, *Proc. Chem. Soc.*, 309 (1959).

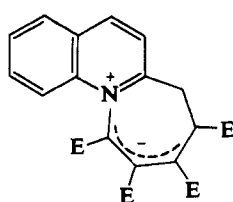
considered to have structure **306**, and subsequently³⁷² **307**, but it was clear that Diels was still not satisfied with this formulation. The unlikely structure **308** was then proposed by Crabtree *et al.*³⁷⁴ as the methyl group attached to the quinoline had disappeared and the presence of a $-\text{CH}_2\text{CH}=<$ grouping was deduced from the NMR spectrum. Although this conclusion was right, the spectrum had been incorrectly analyzed as it was falsely assumed to be first order. Spectra of many such compounds from alkylquinolines, DMAD, and DEAD have now been analyzed and computer simulated,³⁷⁵ and there is no doubt about the presence of the



(306)

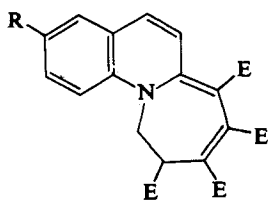
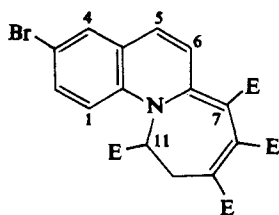


(307)

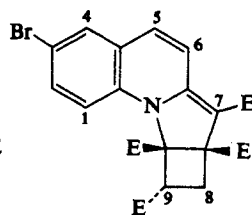


(308)

$-\text{CH}_2\text{CH}=<$ grouping. Because of this, the highly conjugated UV and visible spectra, and for several other reasons, azepine structures (e.g., **309**) were suggested for these compounds.³⁷⁵ 6-Bromo-2-methylquinoline gave two isomeric azepines of almost identical UV and mass spectra. The proton NMR spectrum of one, formulated as **310** was very similar to that of **309**. The other possessed a similar $-\text{CH}_2\text{CH}=<$ system, but with different chemical shifts and coupling constants. The 1-ester-methyl group and the 1-proton were at high field. These data were accommodated by structure **311**,³⁷⁵ but, although satisfactory schemes for the formation of **310** were devised,³⁷⁶ this could not be done


 (309) R = H
 (310) R = Br


(311)



(312)

³⁷⁴ A. Crabtree, L. M. Jackman, and A. W. Johnson, *J. Chem. Soc.*, 4417 (1962).

³⁷⁵ R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc. C*, 362 (1968).

³⁷⁶ R. M. Acheson and D. F. Nisbet, *J. Chem. Soc. C*, 3291 (1971).

for **311**.³⁷⁷ An X-ray structure determination demonstrated that compound **311** actually possesses structure **312**, and ¹³C NMR studies³³⁷ have shown subsequently that most compounds previously considered to be azepines corresponding to **309** are, in fact, tetracyclic and related to **312**. Numerous other products have subsequently been obtained from these reactions, the course of which are strongly solvent-dependent, and these include genuine azepines and deep red and blue adducts structurally related to **312**.

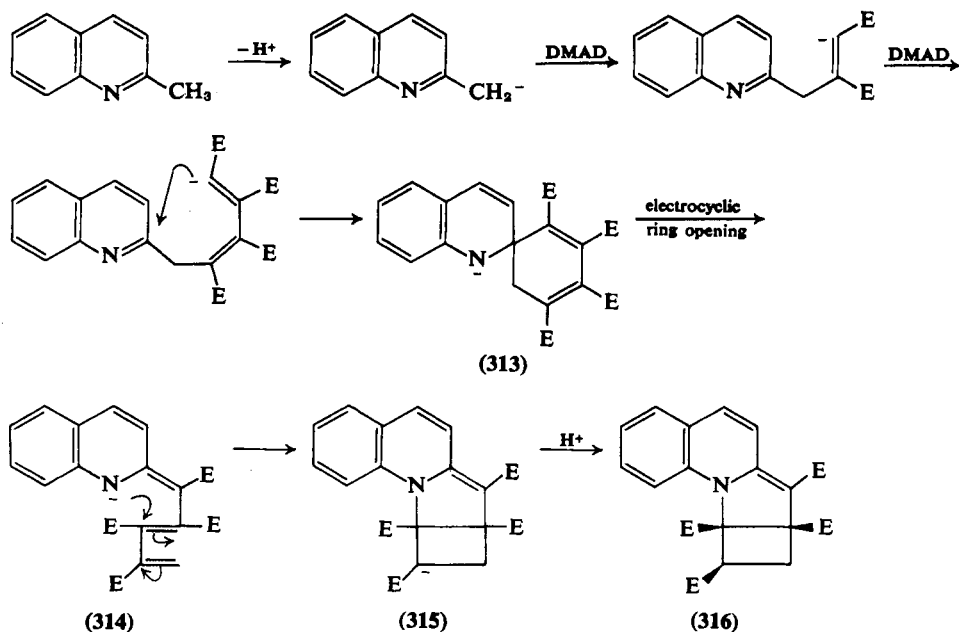
Reactions in Ether and Acetonitrile. Table I summarizes the main products isolated from 2-alkylquinolines and DMAD. In ether or acetonitrile the main products obtained are quinolizines (e.g., **306**), formed by stepwise addition of 2 moles of the acetylene and starting at the nitrogen atom, and cyclobutapyrroloquinolines (**316**), where the ester groups attached to the four-membered ring are all *cis*. In a few instances an isomer with one of the ester groups *trans* (**312**) is also isolable. The *trans* ester-methyl group is in the shielding region of the aromatic carbocyclic ring, and the 1-proton of the aromatic system is in the shielding region of the 9-ester carbonyl group, accounting for their high-field resonances in the NMR spectrometer. The formation of these complex quinolines (Scheme 6) may proceed through loss of a proton from the activated 2-methyl group of the quinoline and addition of 2 moles of DMAD to give the spiro compound **313**. This can then undergo an electrocyclic ring opening, well known in the dihydropyridine series,³⁷⁸ to give **314**, which can then zip up, by two Michael-type reactions, to yield the carbanion **315**. Protonation now gives mainly the least-hindered all-*cis* isomer shown. Tracer experiments³⁷⁷ using methyl-¹³C-labeled 6-bromo-2-methylquinoline, and 2-methylquinoline, have shown that the labeled carbon is attached to two hydrogen atoms in the resulting cyclobutapyrroloquinolines in accordance with the Scheme 6.

If methanol is employed as reaction medium, quinolizines (e.g., **306**) are not formed but relatively high yields of deep red 1:3-molar adducts from the quinoline and DMAD are obtainable.³⁷⁹ Two isomeric types of adducts are formed, which are called "first" and "second" red adducts because of their elution order on chromatography. These adducts proved extremely difficult to separate completely. A provisional structure (**317**), for which many geometrical isomers are possible, was put forward³⁷⁹ to account for the properties of the compounds, but an X-ray diffraction study has now shown that the

³⁷⁷ R. M. Acheson and R. F. Flowerday, *J. Chem. Soc., Perkin Trans. 1*, 394 (1975).

³⁷⁸ E. N. Marvell and I. Shahidi, *J. Am. Chem. Soc.* **92**, 5646 (1970) and earlier papers.

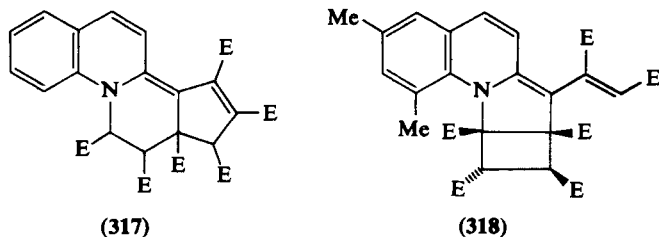
³⁷⁹ R. M. Acheson and D. F. Nisbet, *J. Chem. Soc., Perkin Trans. 1*, 1338 (1973).



SCHEME 6

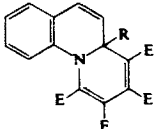
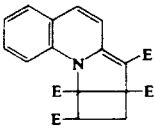
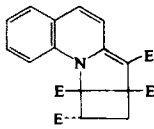
first red adduct from 2,6,8-trimethylquinoline is, in fact, **318**.³⁸⁰ The isomeric adducts may differ only in the configuration of the exocyclic double bond. These adducts (**319**) resemble in structure the 1:2-molar adducts exemplified by **316** and could be formed by similar reactions in which proton transfer occurs instead of spiro-ring formation (Scheme 7).

Quinaldine also yields a purple adduct with 3 moles of DMAD less MeOH, and a deep blue with 4 moles of DMAD less MeOH. X-Ray



³⁸⁰ P. J. Abbott, R. M. Acheson, R. A. Forder, D. J. Watkin, and J. R. Carruthers, *Acta Crystallogr., Sect. B* **33**, 898 (1977).

TABLE I

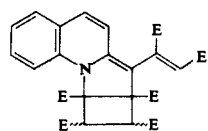
		Types of		
Quinoline	Solvent			
		A	B	C
				
2-Me	Et ₂ O	+	+	
	MeCN	+	+	
	MeOH		+	
2,3-Me ₂	MeCN	+	+	+
2,4-Me ₂	Et ₂ O or	+	+	
	MeCN			
	MeOH			
2,6-Me ₂	MeCN	+	+	
2,8-Me ₂	MeCN	+	+	
	THF			
	C ₆ H ₆			
	MeOH			
2,4,6-Me ₃	MeCN	+	+	
2,4,6,8-Me ₄	MeCN	+		
2,6,8-Me ₃	MeCN			
6-Br-2-Me	Et ₂ O	+	+	+
7-Br-2-Me	Et ₂ O		+	
8-Br-2-Me	Neat 200°			
4-Cl-2-Me	MeCN	+	+	
2-Et	MeCN		+	+
2-PhCH ₂	MeCN	+	+	
2-CH ₂ OMe	Et ₂ O	+		
2-iPr	MeCN	+		
2-PhCH=CH—	PhMe	+		
3-Ph-2-Me	MeCN	+	+	
2,3-[-(CH ₂) ₃ -]	MeCN	+		
2,3-[-(CH ₂) ₄ -]	MeCN	+		

^a Types of product actually isolated are indicated by +.

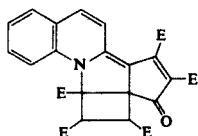
^b Detected by thin-layer chromatography.

PRODUCTS FROM QUINOLINES WITH DMAD^a

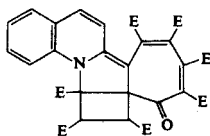
product isolated



D



E



F

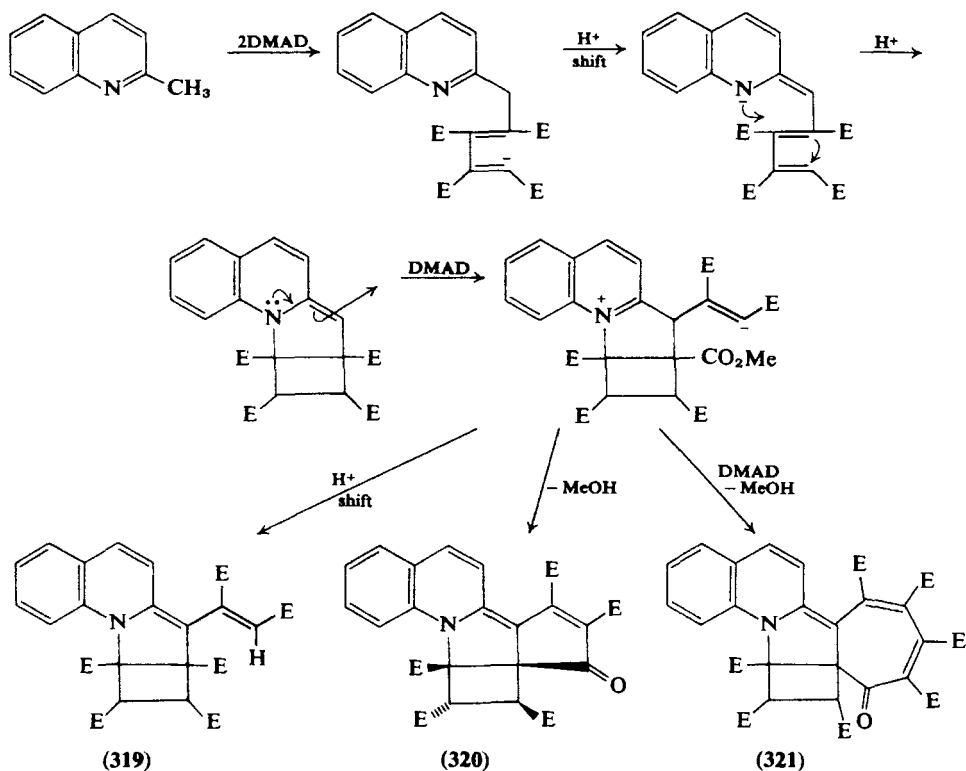
 Attack on
CH₂ only
[e.g., 324
(Section V,G,2)].

G

Other

Ref.

+				+	375
+					375
+	+	+			379
				+	376
					375
+					379
+	+	+			379
+	+		+	+	379
+	+		+	+	379
+	b	b			379
					379
			+	+	379
+	+		+	+	379
					375
					375
			+		375
					376
	+				376
					376
					375
					369
					369
				+	376
			+	+	369
				+	369



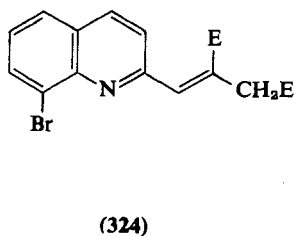
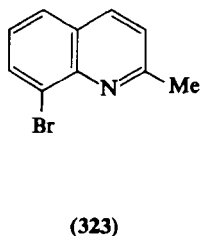
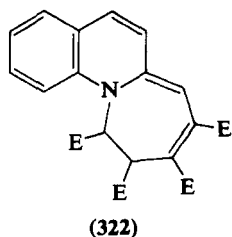
SCHEME 7

studies³⁸¹ show that the purple compound is **320**, but the more conjugated UV spectrum and the ^{13}C NMR spectrum of the deep blue adduct suggest it may be **321**. It is noteworthy that the stereochemistry of the predominantly formed adducts of types **318** and **320** are the same, but differ from **316**, and all possess structures with minimum steric hindrance. It is interesting that the 5:4 ring system, which has a general structural relationship to the penicillin skeleton, is formed so easily in these reactions.

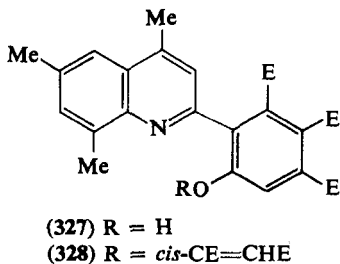
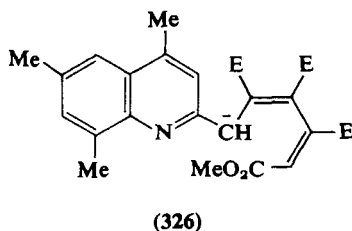
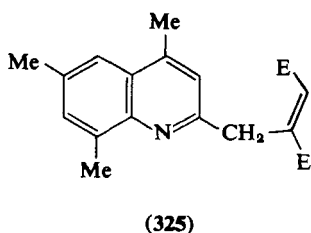
2-Methylquinolines with DEAD give far fewer isolable products than with DMAD, and in some cases different types of adduct are isolated. For instance, 2-methylquinoline itself yields no 6a-methyl-6aH-quinolizine derivative (cf. **306**), but instead gives a cyclobutapyrroloquinoline (cf. **316**) and an azepine (**322**)³⁷⁵ comparable to similar compounds

³⁸¹ P. J. Abbott, R. M. Acheson, R. A. Forder, D. J. Watkin, and J. R. Carruthers, *Acta Crystallogr., Sect. B* **32**, 1927 (1976).

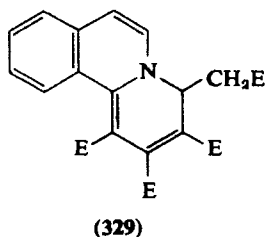
obtained from benzimidazoles and benzothiazoles and formed in the same way.



Steric hindrance from substituents at the 8-position of a 2-methylquinoline inhibits reactions of the nitrogen atom. The quinoline **323** only reacts with DMAD at 200° and yields **324** as sole product.³⁷⁵ In the case of 2,4,6,8-tetramethylquinoline, the analog of **324** and also its presumed precursor (**325**) formed by proton addition to an intermediate carbanion (cf. Scheme 6) were isolated along with **328**.³⁷⁹ This last could be formed via an intermediate (cf. Scheme 6) undergoing proton transfer to **326**, cyclization to a phenol (**327**), and addition to another mole of DMAD.³⁷⁹ 2,8-Dimethylquinoline in tetrahydrofuran with DMAD yielded some of the phenol corresponding to **327**.³⁷⁹

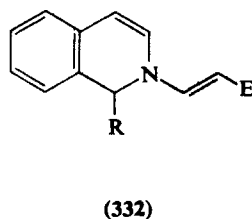
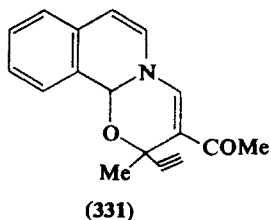
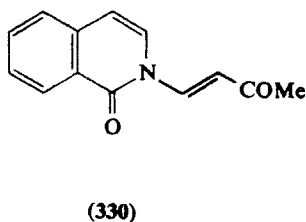


1-Methylisoquinoline with DMAD in ether gives a cyclobutapyrroloisoquinoline (cf. **316**)³⁷⁵ and yet another type of product (**329**) which could be formed via a complex scheme with an ester shift.^{318,375}



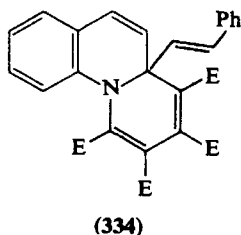
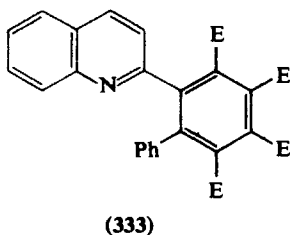
3. Quinoline and Isoquinoline with MP

Quinoline and isoquinoline with MP in ether yield benzoindolizines,³⁸² on exact analogy with the pyridine series. Isoquinoline with but-1-yn-3-one in acetonitrile give the isoquinolone **330**, doubtless due to the presence of traces of water, but in ether an uncommon reaction giving an oxazine (**331**) is observed.²⁹⁹ In the presence of proton donors, isoquinoline behaves like pyridine with MP^{241,382} or but-1-yn-3-one,²⁹⁹ but the anion only reacts at position 1, giving products such as **332**. The anion adds at position 4 in a few similar reactions involving quinolines.^{241,299}



4. Other Quinolines and Acetylenic Esters

2-Styrylquinoline with DMAD in toluene yields some **333**, presumably via cycloaddition to the side chain and dehydrogenation, as well as the 4aH-quinolizine **334**³⁸⁹; the reaction with methyl 2-quinolylacrylate has been mentioned earlier.²⁶⁴

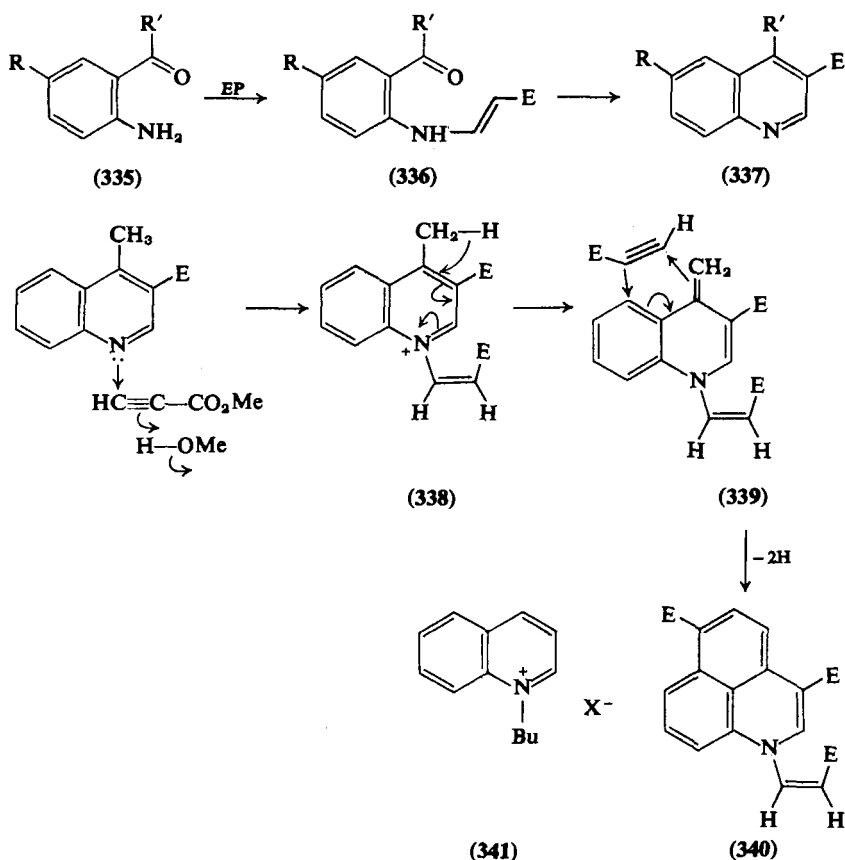


³⁸² R. M. Acheson and M. S. Verlander, *J. Chem. Soc. C*, 2311 (1969).

The synthesis of 2-methyl-1,10-phenanthroline starting from 8-amino-2-methylquinoline was achieved by Heindel and Ohnmacht³⁸³ by a seven-stage sequence, using DMAD.

2-Hydrazinoquinoline behaves with DMAD³⁸⁴ like 1-hydrazinoisoquinolines (see Section V,G,8).

Heindel *et al.*³⁸⁵ have described a synthesis of quinolines (337) beginning with 2-aminophenones (335) and EP. The product (337) from 2-aminoacetophenone added a further 2 moles of propiolate to give 340; the proposed mechanism involving 338 and 339 is shown in Scheme



SCHEME 8

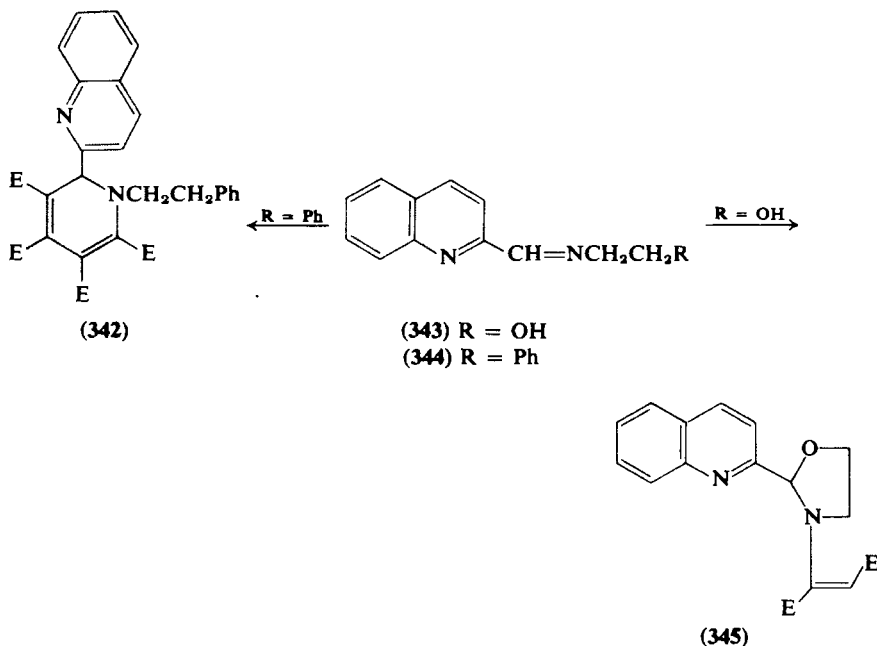
³⁸³ N. D. Heindel and C. J. Ohnmacht, *J. Heterocycl. Chem.* **5**, 869 (1968).

³⁸⁴ M. D. Nair, *Indian J. Chem.* **9**, 104 (1971).

³⁸⁵ N. D. Heindel, P. D. Kennewell, and C. G. Ohnmacht, *J. Org. Chem.* **33**, 1168 (1968).

8. A kinetic study of the addition of hydrogen iodide to DMAD and EP in the presence of 1-butylquinolinium (**341**) appears to show that the quinoline is involved in the reaction.³⁸⁶

Sakamoto and Tomimatsu³⁸⁷ have added Schiff's bases **343** and **344** to DMAD and obtained adducts **345** and **342**. The formation of



dihydropyridines similar to **342** from Schiff's bases and DMAD has been well-documented.^{388,389}

5. Quinoline N-Oxides

The 1,3-dipolar cycloaddition between quinoline-1-oxide (**346**) and methyl propiolate in the presence of acetic anhydride and hydroquinone gave **348** via **347**.³⁹⁰

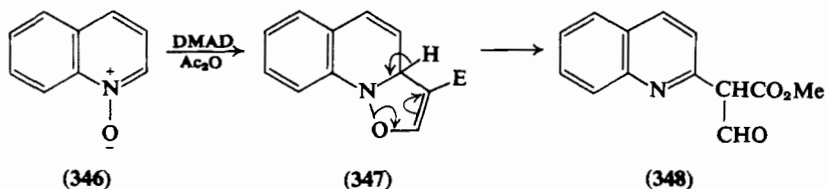
³⁸⁶ G. F. Dvorko and T. F. Karpenko, *Ukr. Khim. Zh.* **31**, 75 (1965) [*CA* **62**, 14,465 (1965)].

³⁸⁷ M. Sakamoto and Y. Tomimatsu, *J. Pharm. Soc. Jpn.* **90**, 1339 (1970) [*CA* **74**, 53,468 (1971)].

³⁸⁸ J. M. F. Gagan, *J. Chem. Soc. C*, 1121 (1966).

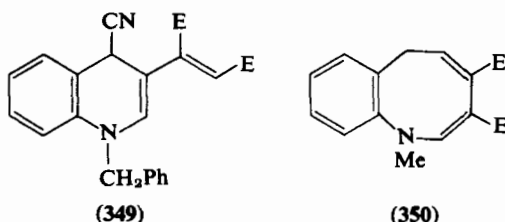
³⁸⁹ R. Huisgen and K. Herbig, *Annalen* **688**, 98 (1965).

³⁹⁰ M. Hamana, K. Funakoshi, H. Shigyo, and Y. Kuchino, *Chem. Pharm. Bull.* **23**, 346 (1975).

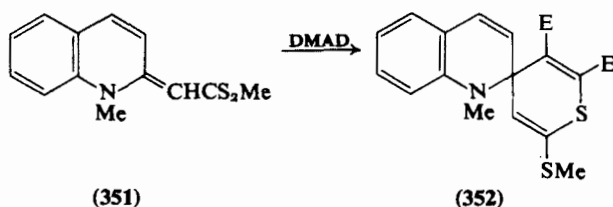


6. Dihydroquinolines

1-Benzyl-4-cyano-1,4-dihydroquinoline yields **349** with the ester,²⁸¹ and 1-methyl-1,4-dihydroquinoline gives the azocine **350**, a cyclobutene intermediate being detected.³⁹¹ This contrasts with the 1,4-dihydropyridine series where the cyclobutene is stable.



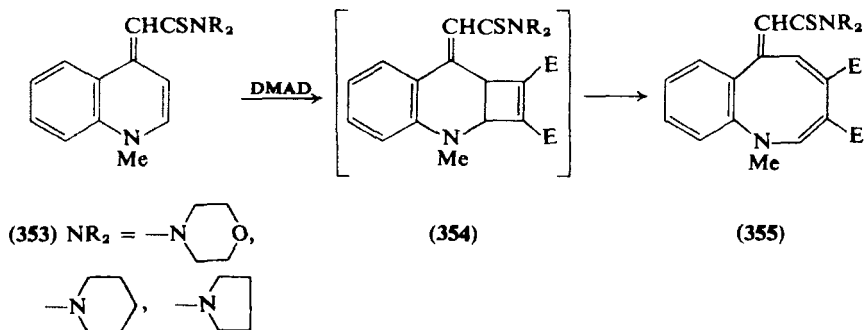
Kobayashi *et al.*³⁹² have studied the 1,4-dipolar cycloadditions of DMAD to enaminodithiocarboxylates derived from dihydroquinolines. Addition of acetylene to **351** gave the spirocycloadduct **352** which did



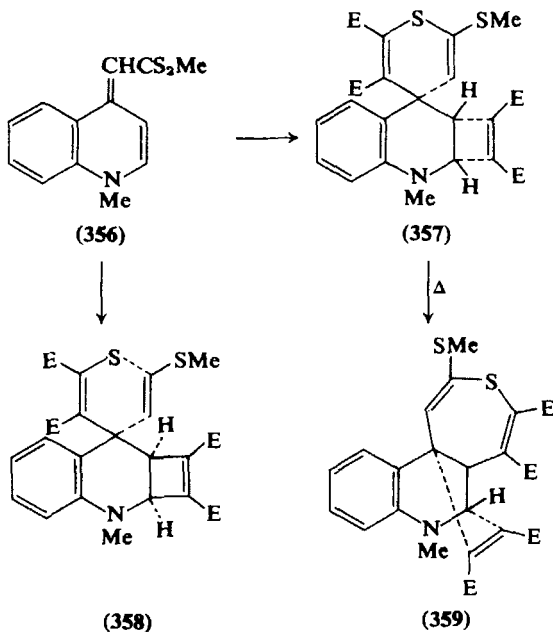
not extrude sulfur by analogy with the corresponding thazolines (see Section X,F). The thioamides **353** derived from 4-methylquinoline add DMAD in an enaminic manner, forming unstable cyclobutenes (**354**) which rearrange to **355**. The analogous dithiocarbamate ester (**356**) gave

³⁹¹ P. G. Lehman, *Tetrahedron Lett.*, 4863 (1972).

³⁹² G. Kobayashi, Y. Matsuda, Y. Tominaga, and K. Mizuyama, *Chem. Pharm. Bull.* **23**, 2749 (1975).

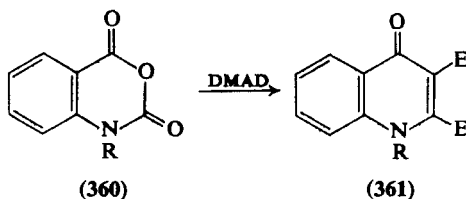


two isomeric 1:2-molar adducts (357 and 358), and an interesting rearrangement was observed when 357 was heated, leading to 359; compound 358 did not undergo this transformation.



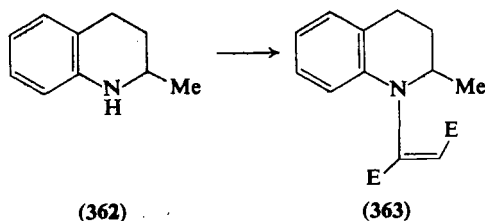
Taylor and Heindel reacted several substituted *o*-aminobenzophenones and *o*-aminoacetophenones with DMAD; the yields of the quinolones produced depend on the basicity of the starting amino compounds. They also reacted isatoic anhydrides (360) with DMAD in basic methanolic medium to obtain 4-quinolones (361).³⁹³

³⁹³ E. C. Taylor and N. D. Heindel, 147th Am. Chem. Soc. Meeting, Philadelphia, 1964, Abstr. 8M; *J. Org. Chem.* 32, 3339 (1967).

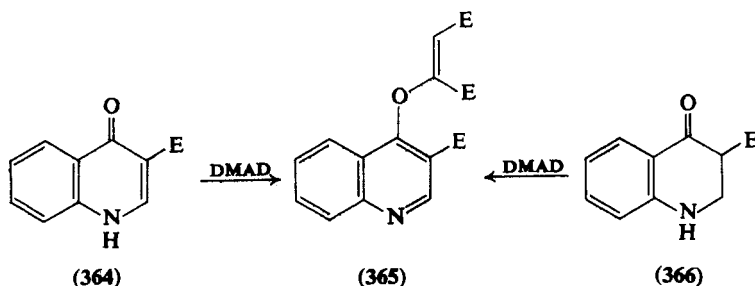


7. Tetrahydroquinolines

The addition of DMAD to 2-methyl-1,2,3,4-tetrahydroquinoline (362) gave 363.³⁹⁴



Both methyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (364) and the corresponding tetrahydro derivative (366) gave the same adduct (365) with DMAD. There was no evidence of *N*-alkylation even with 366, which was refluxed in toluene for 24 hours with the dienophile.³⁹⁵



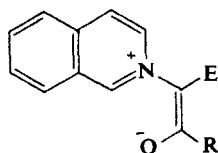
8. Other Isoquinolines with Acetylenic Esters

Isoquinoline *N*-oxide with DMAD and DEAD gave 367 and with EPP, 368.³⁹⁶

³⁹⁴ M. N. Sharma, *Curr. Sci.* **42**, 201 (1973) [*CA* **78**, 159,390 (1973)].

³⁹⁵ G. R. Proctor, W. I. Ross, and A. Tapia, *J. Chem. Soc., Perkin Trans. 1*, 1803 (1972).

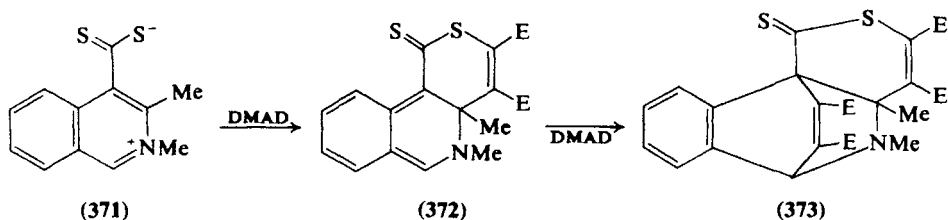
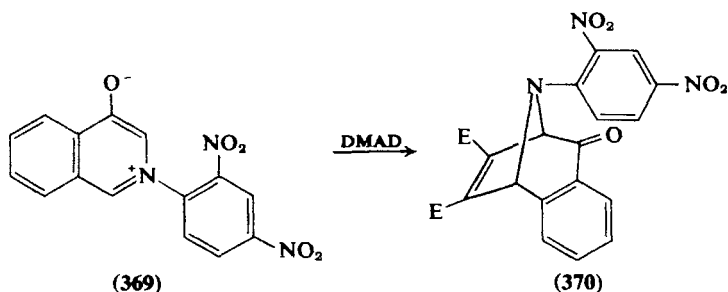
³⁹⁶ R. Huisgen, H. Seidl, and J. Wulff, *Chem. Ber.* **102**, 915 (1969).



(367) R = E

(368) R = Ph

The addition of DMAD to the isoquinolinium betaine **369** gave the interesting cycloadduct **370**.³⁹⁷ A 1,4-cycloaddition and Diels-Alder reaction took place when 4-dithiocarboxyl-2,3-dimethylisoquinolinium betaine (**371**) was heated with DMAD in DMF for 20 to 30 minutes at 100°. The initial product was thought to be **372**, which added a second mole of ester yielding **373**.³⁹⁸



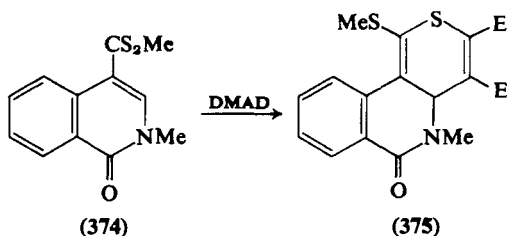
The related isoquinolone **374** also adds DMAD to give a product (**375**) similar to the postulated **372**.³⁹²

Phenylpropionic ester with 1-hydrazino-3-methylisoquinoline gave (**376**), identified by X-ray crystallography,³⁹⁹ and a similar product has been obtained from 3-chloro-1-hydrazino-6-nitroisoquinoline and

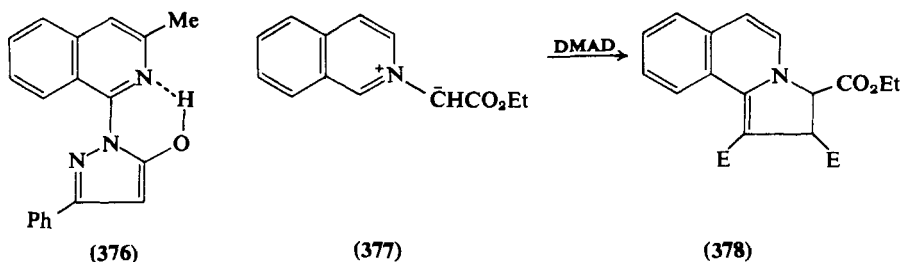
³⁹⁷ N. Dennis, A. R. Katritzky, and S. K. Parton, *Chem. Pharm. Bull.* **23**, 2899 (1975).

³⁹⁸ K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles* **2**, 611 (1974) [*CA* **82**, 43,213 (1975)].

³⁹⁹ G. S. D. King and H. Reimlinger, *Chem. Ber.* **104**, 2694 (1971).



DMAD.³⁰⁷ 1-Hydrazinoisoquinoline is alleged to give the corresponding hydrazide³⁸⁴ with phenylpropiolyl chloride, but the product is probably a pyrazolone (cf. 376).



Zugravescu *et al.*⁴⁰⁰ heated isoquinoline with diazoacetic ester in chloroform. The resulting stable red intermediate (377) with DMAD gave 378, which on heating aromatized to 383.⁴⁰¹

Basketter and Plunkett⁴⁰² reacted isoquinolinium ylids (379–382) with DMAD and isolated the 2,3-dihydrobenzo[g]indolizines 386–389 as well as the expected benzo[g]indolizines 383–385. Addition of MP to 379–382 gave the benzoindolizines but no dihydro compounds. Subsequently,⁴⁰³ these same workers reported an anomalous product 390 from 380 with DMAD in methanol. Japanese investigators have described very similar work.^{404–407}

⁴⁰⁰ I. Zugravescu, E. Rucinski, and G. Surpateanu, *Tetrahedron Lett.*, 941 (1970).

⁴⁰¹ D. G. Farnum, R. J. Alaimo, and J. M. Dunston, *J. Org. Chem.* **32**, 1130 (1967).

⁴⁰² N. S. Basketter and A. O. Plunkett, *Chem. Commun.*, 1578 (1971).

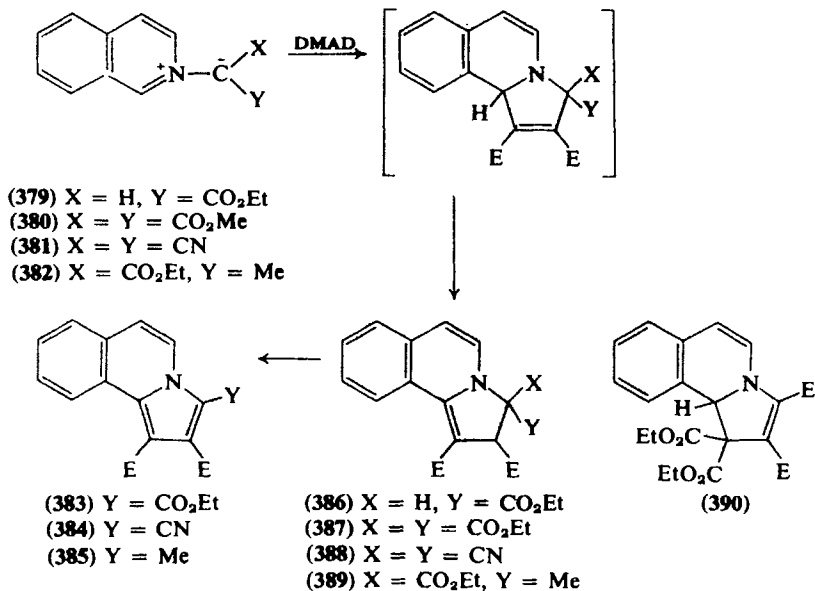
⁴⁰³ N. S. Basketter and A. O. Plunkett, *Chem. Commun.*, 594 (1975).

⁴⁰⁴ T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.* **20**, 1558 (1972).

⁴⁰⁵ T. Kutsuma, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.* **20**, 1809 (1972).

⁴⁰⁶ T. Kutsuma, Y. Sekine, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.* **20**, 2701 (1972).

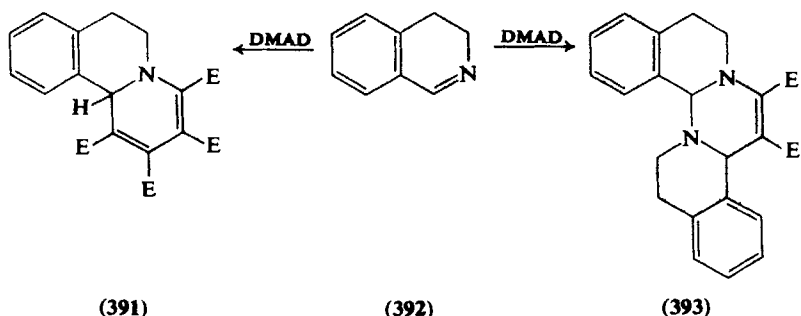
⁴⁰⁷ Y. Kobayashi, I. Kumadaki, Y. Sekine, Y. Naito, and T. Kutsuma, *Chem. Pharm. Bull.* **23**, 566 (1975).



Isoquinoline ylids (e.g., 381) also give indolizines with allenes.²⁸¹

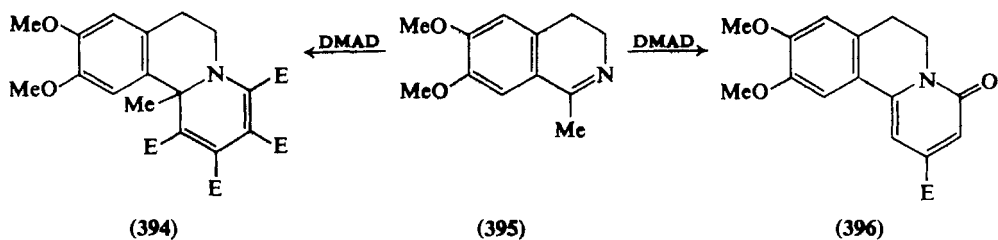
9. Dihydroisoquinolines

Huisgen and Herbig³⁸⁹ reacted 3,4-dihydroisoquinoline (392) with DMAD and isolated the 1:2- and 2:1-molar adducts 391 and 393.

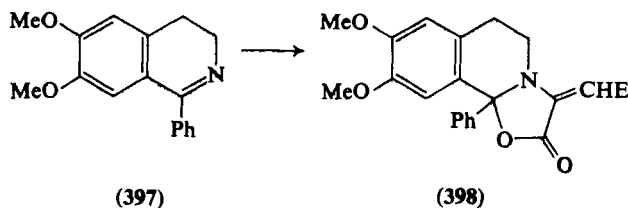


Nair⁴⁰⁸ treated several 1-methyl-3,4-dihydroisoquinolines (e.g., 395) with DMAD and DEAD and found that the products depend on the solvent used. In ether, a 1:2-molar adduct (394) formed, whereas a 1:1-molar adduct (396) was obtained in methanol.

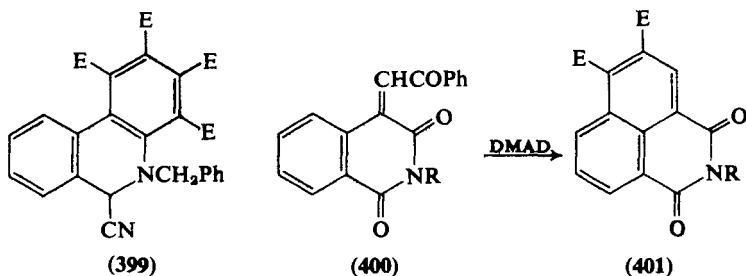
⁴⁰⁸ M. D. Nair, *Indian J. Chem.* 6, 630 (1968) [*CA* 70, 47,265 (1969)].



1-Phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (397) with DMAD in methanol gave only 398.^{408,409} A similar reaction has been reported by Grovenstein and co-workers with 2-phenylquinoxaline.⁴¹⁰ The IR band at 1785 cm^{-1} is considered⁴⁰⁸ to indicate a lactone.



2-Benzyl-1-cyano-1,2-dihydroisoquinoline behaves quite differently to the isomeric quinoline (Section V,G,6) and through cycloaddition and dehydrogenation yields 399.²⁸¹ Isoquinolinediones (400 R = H and Me)



with DMAD give low yields of the tricyclic compounds 401.⁴¹¹

3,4-Dihydroisoquinoline N-oxide with DMAD, EP, and EPP gave 402, 403, and 404, respectively.^{412,413}

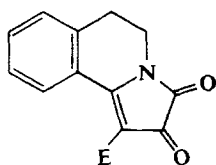
⁴⁰⁸ M. D. Nair, *Indian J. Chem.* **6**, 226 (1968).

⁴¹⁰ E. Grovenstein, W. Postman, and J. W. Taylor, *J. Org. Chem.* **25**, 68 (1960).

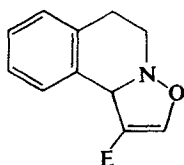
⁴¹¹ R. M. Acheson, A. S. Bailey, and P. C. Bell, *J. Chem. Soc. C*, 1709 (1968).

⁴¹² H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.* **102**, 904 (1969).

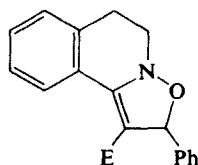
⁴¹³ R. Huisgen, H. Seidl, and I. Bruening, *Chem. Ber.* **102**, 1102 (1969).



(402)

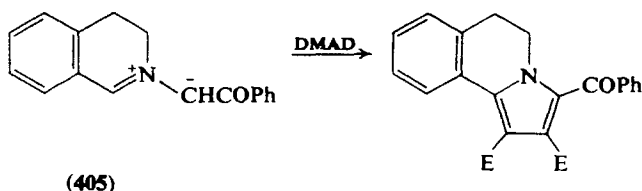


(403)



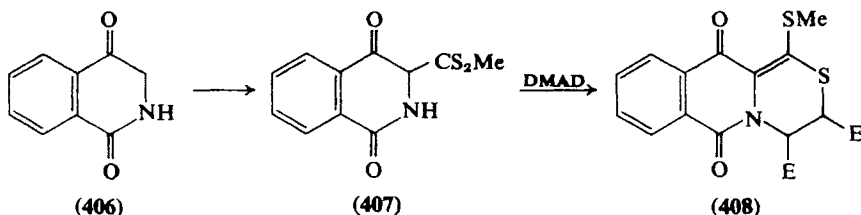
(404)

Addition of DMAD and EP to the ylid **405** has also been described.⁴¹⁴



(405)

Ueno *et al.*⁴¹⁵ reacted 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline (**406**) with carbon disulfide, then methylated to **407**, which, with DMAD and potassium carbonate in DMF, gave dimethyl 6,11-dioxo-1-methylthio-3,4,6,11-tetrahydro[1,4]thiazino[4,3-*b*]isoquinoline-3,4-dicarboxylate (**408**).



(406)

(407)

(408)

Dyke and co-workers^{416,417} found that the isocarbostyryls **409** and **412** with propiolic acid gave the diphenyls **410** and **411**.

H. PHTHALAZINES

No crystalline products were formed from phthalazine and DMAD in benzene or acetonitrile, but in methanol **413** was obtained.⁴¹⁸

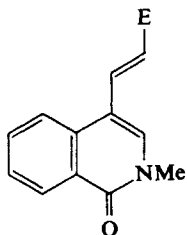
⁴¹⁴ R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

⁴¹⁵ S. Ueno, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *J. Pharm. Soc. Jpn.* **94**, 607 (1974) [*CA* **81**, 120,391 (1974)].

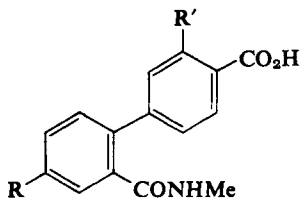
⁴¹⁶ S. F. Dyke, M. Sainsbury, D. W. Brown, and R. D. J. Clipperton, *Tetrahedron* **26**, 5969 (1970).

⁴¹⁷ S. F. Dyke, P. A. Bather, and D. W. Wiggins, *Tetrahedron* **29**, 3881 (1973).

⁴¹⁸ R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 2218 (1966).

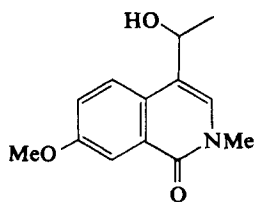


(409)



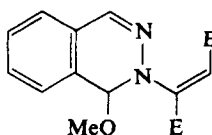
(410) R = H, R' = E

(411) R = OMe R' = H

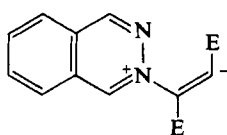


(412)

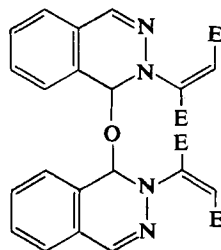
Reaction in ether is stated⁴¹⁹ to give the ylid **414**, but further investigations⁴²⁰ have shown that the supposed ylid is, in fact, the ether **415**, which could be formed from the ylid and traces of water present in the ether used.



(413)

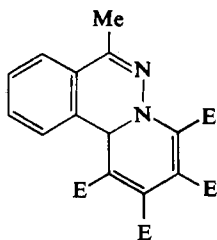


(414)

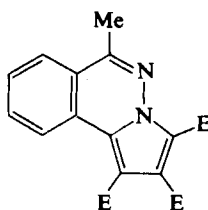


(415)

4-Methylphthalazine in acetonitrile gave **416** and **417**, initial attack having taken place on the less hindered nitrogen atom.⁴¹⁸



(416)

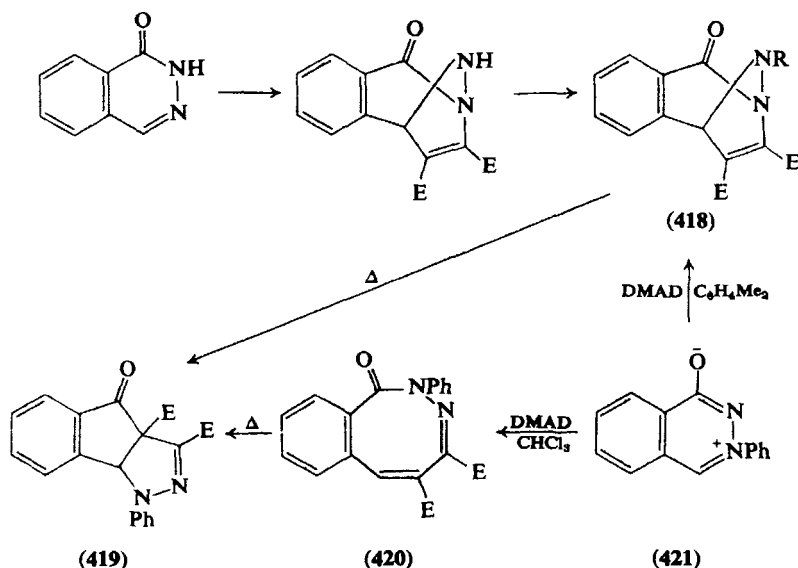


(417)

⁴¹⁹ M. Petrovanu, A. Saucive, I. Gabe, and I. Zugravescu, *Rev. Roum. Chim.* **13**, 513 (1968).

⁴²⁰ R. M. Acheson and R. T. Aplin, unpublished work.

1(2*H*)-Phthalazinone with DMAD gave the 1:2-molar adduct **418** ($R = \textit{trans}\text{-CE=CHE}$) formed by the sequence outlined.⁴²¹ 3-Phenyl-1-oxidophthalazinium betaine (**421**), which is more reactive than the 3-methyl analog toward olefins, with DMAD in refluxing xylene, gave **418** ($R = \text{Ph}$), but in chloroform **420** was obtained.^{421a} On heating alone, both **418** and **420** rearranged to **419**; the mechanisms whereby these interesting transformations occur have not yet been ascertained.^{421a}



Addition of DMAD to 1-hydrazinophthalazine (**422**) gave **423** which cyclized in base to **424** and gave the isomer **425** with acid.³⁰⁸ These results contrast with those of Nair³⁰⁷ who states that **422** and DMAD give **426**.

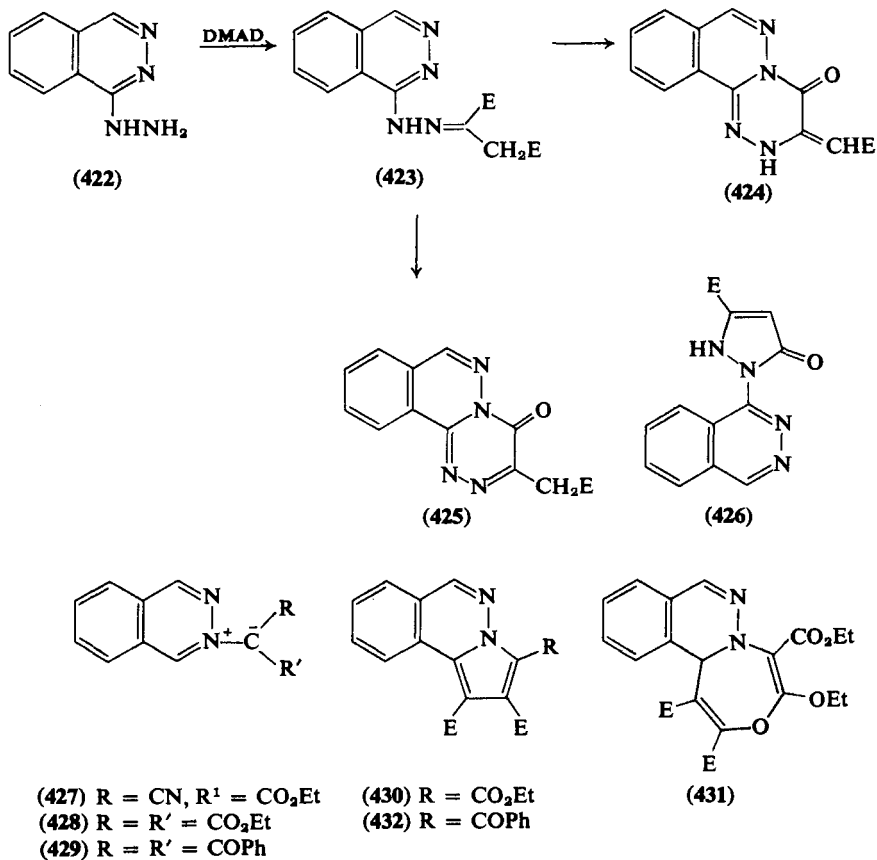
The phthalazine ylids **427–429** gave the adducts **430**, **431**, and **432**, respectively, with DMAD⁴²²; the 4-methyl derivative of **429** reacted similarly.⁴²³

⁴²¹ M. Ramaiah, Ph.D. Thesis, University of East Anglia, 1974; quoted in N. Dennis, A. R. Katritzky, and Y. Takeuchi, *Angew. Chem., Int. Ed. Engl.* **15**, 1 (1976).

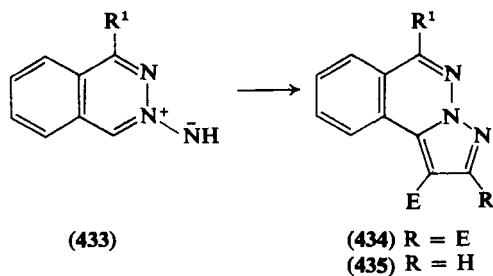
^{421a} N. Dennis, A. R. Katritzky, and M. Ramaiah, *J. Chem. Soc., Perkin Trans. 1*, 2281 (1976).

⁴²² M. Petrovanu, A. Saucive, and I. Zugravescu, *Rev. Roum. Chim.* **19**, 437 (1974) [*CA* **81**, 12,723 (1974)].

⁴²³ M. Petrovanu, M. Caprosu, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi, Sect. Ic* **20**, 183 (1974) [*CA* **83**, 9954 (1975)].



Addition of DMAD and MP to the 1-substituted phthalazine-3-imine (433) gave the adducts 434 and 435.⁴²⁴

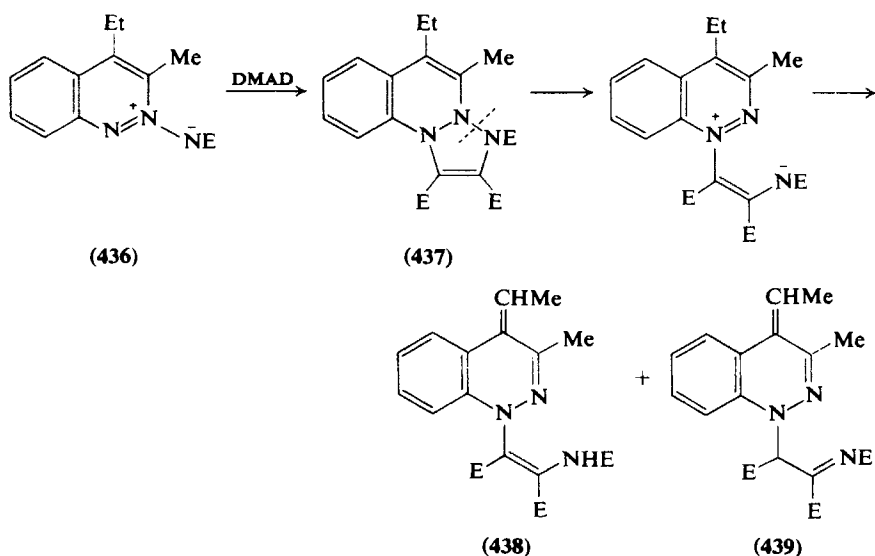


⁴²⁴ Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 119 (1975).

I. CINNOLINES

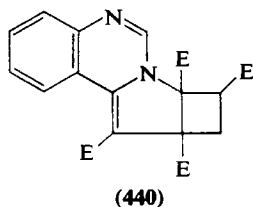
4-Methylcinnoline with DMAD yields a 2:3 molar adduct that has not been identified.⁴²⁵

Cinnoline-2-imine **436** with DMAD yields a mixture of the tautomeric adducts **438** and **439**.⁴²⁶ They are clearly formed by initial cyclization onto the 1-nitrogen atom (**437**), followed by ring scission as shown. The alternative mode of cyclization, onto carbon, although favored in the pyridazine series, is not possible here unless the resonance of both rings is disrupted.



J. QUINAZOLINES

The structure, which contains an azepine ring, given³³⁶ to an adduct from 4-methylquinazoline must be corrected to **440**,³³⁷ and the formula-

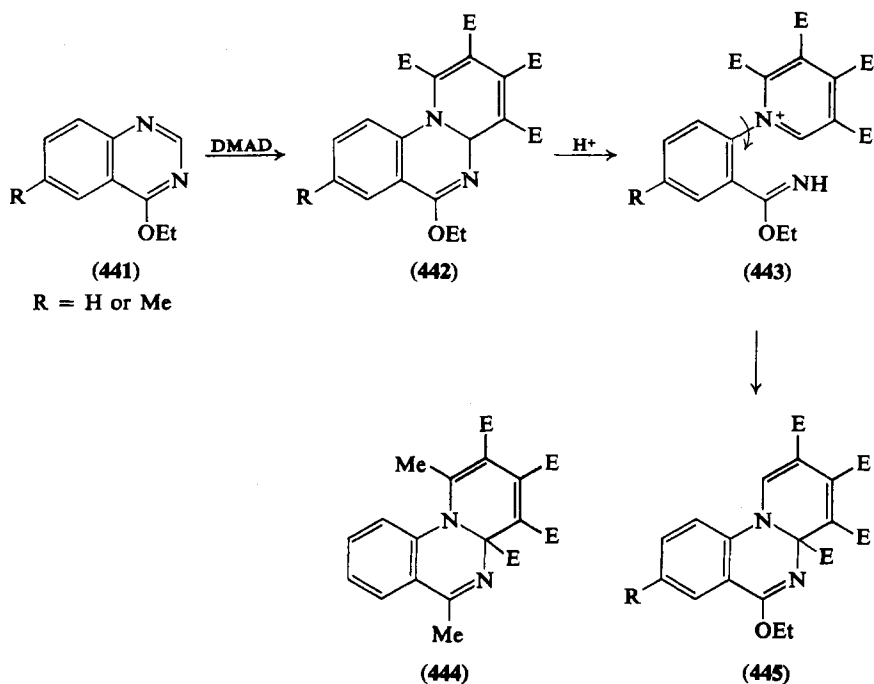


⁴²⁵ R. M. Acheson and M. W. Foxton, unpublished observation.

⁴²⁶ C. W. Rees, R. W. Stephenson, and R. C. Storr, *Chem. Commun.*, 941 (1974).

tion given to the 1:3-molar adduct, a minor product from 2,4-dimethylquinazoline,³³⁸ needs a similar revision.

4-Ethoxyquinazoline, and its 6-methyl derivative (**441**), with DMAD in calcium hydride-dried acetonitrile give **442**, initial attack having taken place from the less hindered nitrogen atom^{427,428}; 4-ethoxy-8-methylquinazoline, where the 1-nitrogen atom is also sterically hindered, does not react. In the presence of a trace of strong acid, adducts **442** undergo a rapid rearrangement to **445** (Scheme 9), as in the thiazole series (see Section X,B). Addition of a proton is probably necessary as the nitrogen atom is less willing to bear a negative charge than sulfur. If the acetonitrile used for the original preparation is distilled over phosphorus pentoxide, it contains sufficient acid to promote the rearrangement. If **445** (R = H) is treated with excess of trifluoroacetic acid in deuteriochloroform, changes in the NMR spectrum, which are reversed



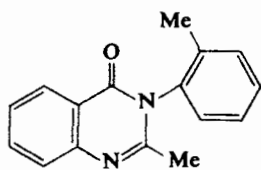
SCHEME 9

⁴²⁷ P. J. Abbott, R. M. Acheson, M. Y. Kornilov, and J. K. Stubbs, *J. Chem. Soc., Perkin Trans. 1*, 2322 (1975).

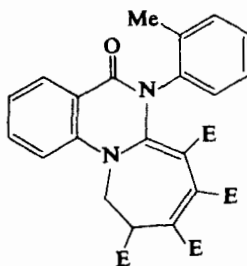
⁴²⁸ R. M. Acheson, P. J. Abbott, J. K. Stubbs, and M. Y. Kornilov, *Khim. Geterotsikl. Soedin.*, 1701 (1975).

by pyridine, suggest that the protonated form of **443** is produced. A study of the europium-induced shifts has shown that the main reaction product from 2,4-dimethylquinazoline and DMAD does not have a structure analogous to **442**³³⁸ but is, in fact, **444**, rearrangement having taken place.⁴²⁸

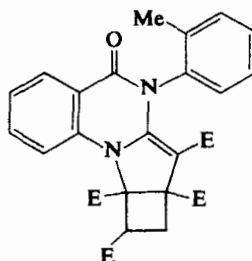
The hypnotic agent methaqualone (**446**) with DMAD in acetonitrile gave 28% of a 1:2-molar adduct formulated as **447**.⁴²⁹ This structure must now (see 2-methylquinoline adducts, Section V,G,2) be revised to **448**, and the structures of various transformation products also require appropriate revision.



(446)

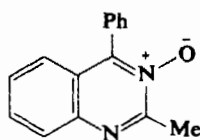


(447)

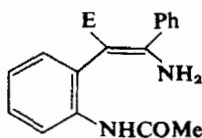


(448)

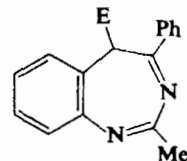
Addition of DMAD and DEAD to 2-methyl-4-phenylquinazoline 3-oxide (**449**) has been described by Strauss *et al.*⁴³⁰ The products are considered to be **450** and **451**.



(449)



(450)



(451)

Ethyl propiolate or DMAD and the quinazoline imine (**452**) give a complex mixture.⁴³¹

⁴²⁹ J. B. Harrison, D. R. Harrison, and F. Fried, *J. Heterocycl. Chem.* **9**, 1227 (1972).

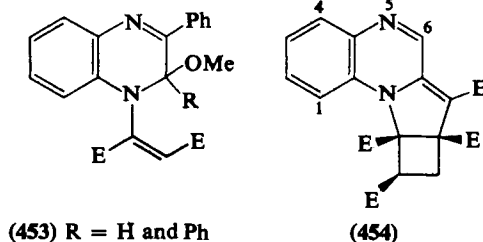
⁴³⁰ U. Strauss, H. P. Harter, M. Neuenschwander, and O. Schindler, *Helv. Chim. Acta* **55**, 771 (1972).

⁴³¹ Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 119 (1975).

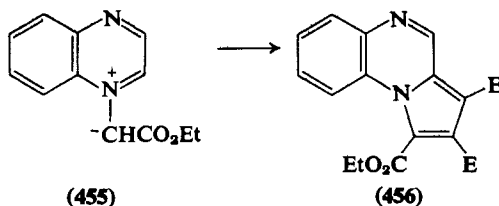


K. QUINOXALINES

2-Phenyl- and 2,3-diphenyl-quinoxalines in methanol with DMAD give 1:1:1 adducts (453),⁴¹⁰ whereas 2-methyl- and 2,3-dimethyl-quinoxalines in acetonitrile form as major products cyclobutapyrroles (454),³³⁷ earlier described⁴³² as azepines. By-products in the last two cases are, respectively, the *r*-7*a*,*t*-9,*c*-9*a*-isomer of 454 and a compound analogous to that formed from 2,3,5,6-tetramethylpyrazine.



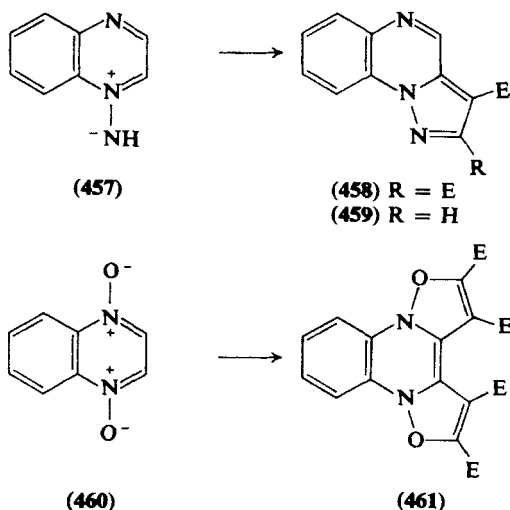
Zugravescu *et al.* have reacted the quinoxaline ylid 455 with DMAD and obtained the 1,3-cycloaddition-oxidation product 456.⁴³³ They also claim the preparation of 461 from quinoxaline di-*N*-oxide (460),⁴³⁴ but isomeric structures do not seem excluded. The quinoxaline imine 457 with DMAD and EP gives 458 and 459, respectively.⁴³¹



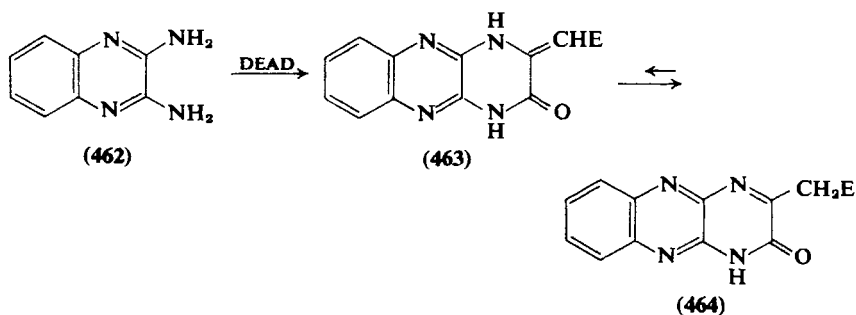
⁴³² R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 378 (1968).

⁴³³ M. Ungureanu, I. Druta, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi, Sect. Ic* 19, 167 (1973) [*CA* 80, 108,478 (1974)].

⁴³⁴ M. Ungureanu, I. Druta, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi, Sect. Ic* 20, 29 (1974) [*CA* 82, 125,351 (1975)].



Diethyl acetylenedicarboxylate with 2,3-diaminoquinoxaline (**462**) in methanol gave pyrazino[2,3-*b*]quinoxaline (**463**), which exists as the tautomer **464** in the solid state. In solution, NMR measurements show that a tautomeric mixture of both **463** and **464** is present.⁴³⁵



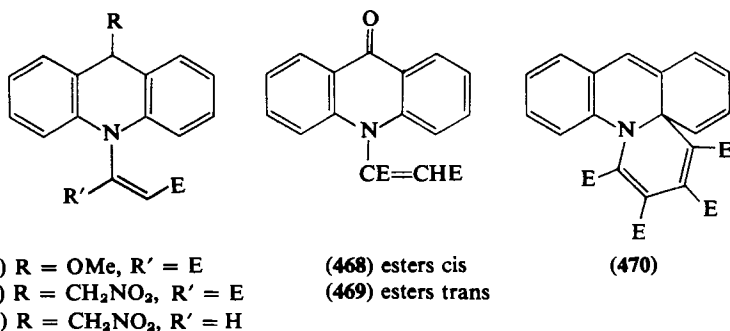
L. ACRIDINES

Acridine with DMAD in methanol yields mainly **465**⁴³⁶; in ether, aerial oxidation also occurs, and the product is a mixture of the acridanones **468** and **469**.⁴³⁶ In nitromethane the products are **468**, **466**, and the deep red **470**,³⁰⁰ previously⁴³⁷ obtained from a reaction conducted

⁴³⁵ E. B. Nyquist and M. M. Joullié, *J. Chem. Soc. C*, 947 (1968).

⁴³⁶ R. M. Acheson and M. L. Burstall, *J. Chem. Soc.*, 3240 (1954).

⁴³⁷ O. Diels and K. Alder, *Annalen* **543**, 79 (1940).

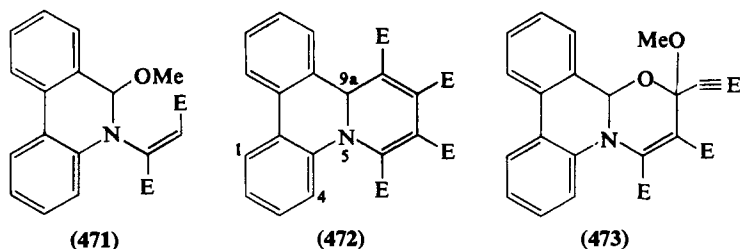


in ether and considered to have another structure. Acridine with MP in nitromethane yields a mixture of *trans*- and *cis*- **467**.³⁰⁰

Benzo[*b*]acridine, which, like anthracene, adds maleic anhydride and other dienophiles across the 6,11-positions of a carbocyclic ring, with DMAD in methanol gives a compound corresponding to **465**.⁴³⁸

M. PHENANTHRIDINES

Phenanthridine with DMAD in dry methanol yields **471**, but if water is present related compounds are also formed.⁴³⁹ In benzene the expected quinolizine **472** and also the oxazine **473** are obtained.^{440,441} Nucleophilic attack at the carbonyl group of DMAD is uncommon.



6-Methylphenanthridine with DMAD in benzene yields the 9a-methyl-9a*H*-quinolizine (cf. **306**, Section V,G,2) and a cyclobuta[4,5]-pyrrolo[1,2-*f*]phenanthridine (cf. **312**, Section V,G,2); DEAD in ether gives the corresponding cyclobuta derivative, whereas 6-ethylphenanthridine with DMAD in acetonitrile yields only the quinolizine as isolable product. With MP, phenanthridine, like pyridine, yields indolizines,

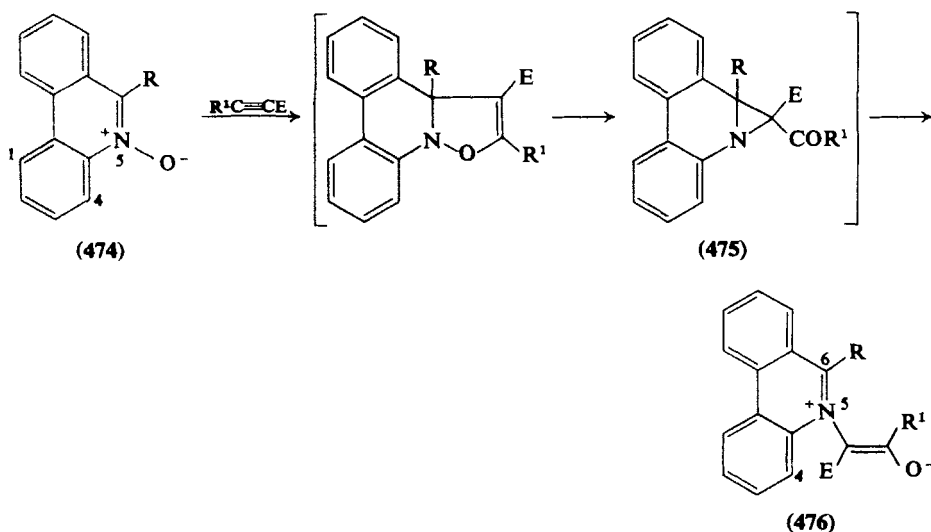
⁴³⁸ R. M. Acheson and C. W. Jefford, *J. Chem. Soc.*, 2676 (1956).

⁴³⁹ R. M. Acheson and G. J. F. Bond, *J. Chem. Soc.*, 246 (1956).

⁴⁴⁰ R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 3785 (1962).

⁴⁴¹ R. M. Acheson, G. R. Miller, and A. O. Plunkett, *J. Chem. Soc.*, 3888 (1963).

and its 6-methyl derivative, dimethyl 9a-methyl-9a*H*-dibenzo[*a,c*]quinolizine-7,9-dicarboxylate (cf. 472).⁴⁴² This is the first example of the addition of MP to a pyridine-type heterocycle without a proton shift taking place. Phenanthridine 5-oxide (474),⁴⁴³ and a variety of 6-substituted derivatives,⁴⁴⁴⁻⁴⁴⁷ combine with MPP to give oxidovinyl-phenanthridinium ylids (476). The reaction probably proceeds as shown,⁴⁴³ the same as in the case of certain isoquinoline 2-oxides,⁴⁴⁸ and an intermediate corresponding to 475 has been isolated.⁵⁰¹ Even the



presence of a methyl group at position 6 prevents the free rotation of the 5-substituent (R' = E),⁴⁴⁶ and both rotational⁴⁴⁹ and geometrical isomerism is observable in suitable cases, for example, when the 6-substituent is *o*-tolyl.⁴⁴⁷

N. BENZOCINNOLINES

In contrast to 4-methylcinnoline, benzo[*c*]cinnoline with DMAD in methanol⁴⁵⁰ or without solvents⁴⁵¹ gave tetramethyl benzo[*c*]pyrida-

⁴⁴² R. M. Acheson and M. S. Verlander, *J. Chem. Soc. C*, 2311 (1969).

⁴⁴³ R. M. Acheson, I. A. Selby, and A. S. Bailey, *Chem. Commun.*, 835 (1966).

⁴⁴⁴ R. M. Acheson, I. A. Selby, and A. S. Bailey, *J. Chem. Soc. C*, 2066 (1967).

⁴⁴⁵ R. M. Acheson and I. A. Selby, *J. Chem. Soc. C*, 691 (1971).

⁴⁴⁶ R. M. Acheson and I. A. Selby, *Chem. Commun.*, 537 (1973).

⁴⁴⁷ R. M. Acheson and I. A. Selby, *J. Chem. Soc., Perkin Trans. 1*, 423 (1974).

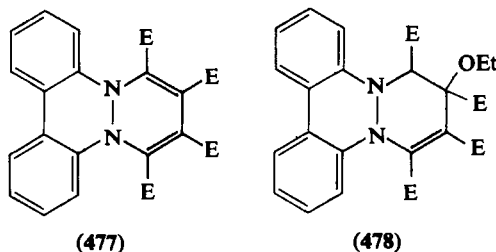
⁴⁴⁸ H. Seidel, R. Huisgen, and R. Knorr, *Chem. Ber.* **102**, 904 (1969).

⁴⁴⁹ R. M. Acheson and I. A. Selby, *Chem. Commun.*, 62 (1970).

⁴⁵⁰ M. W. Foxton, D. Phil. thesis, Oxford University, 1965.

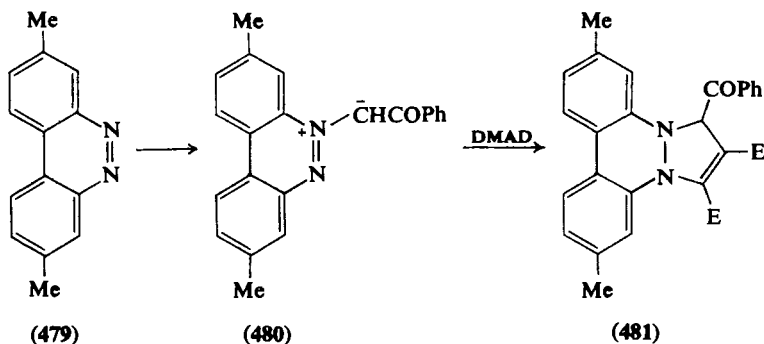
⁴⁵¹ A. N. Hughes and T. Monkoltananont, *Chem. Ind. (London)*, 662 (1967).

zine[1,2-*a*]cinnoline-6,7,8,9-tetracarboxylate (**477**).⁴⁵² Similar results are obtained in dimethylformamide.^{453,454} Attempts to prepare the corresponding adduct from DEAD failed completely, possibly for steric reasons, but in ethanol solution 1:2:1-molar adduct was obtained and tentatively assigned structure **478**.⁴⁵²



Zugravescu *et al.*⁴⁵³⁻⁴⁵⁵ obtained the *N*-phenacyl ylid **480** from **479** and prepared the cycloadduct **481** from the former. Farnum *et al.*⁴⁵⁶ prepared the ylid **482**, showed that **483** was formed from DMAD, and that the NMR spectrum of the compound excluded the alternative structure **484**.

Benzocinnoline imines have been described by Rees *et al.*^{457,458} as a part of their study of azimines as 1,3-dipoles. The imine **485** added



⁴⁵² R. M. Acheson, M. W. Foxton, N. R. Raulins, and G. E. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 2182 (1970).

⁴⁵³ E. Carp, M. Dorneau, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi Sect. 1c* **19**, 1507 (1974) [*CA* **82**, 72,912 (1975)].

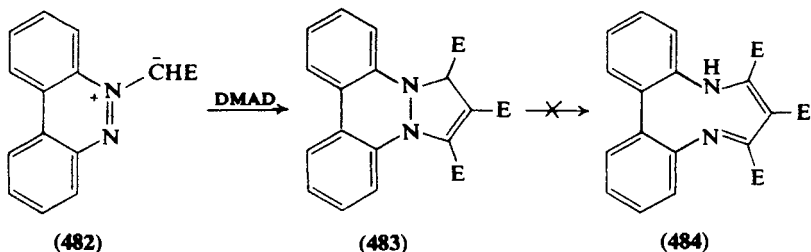
⁴⁵⁴ M. Dorneau, E. Carp, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi Sect. 1c* **19**, 223 (1973) [*CA* **80**, 13,371 (1974)].

⁴⁵⁵ M. Dorneau and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi Sect. 1c* **20**, 35 (1974) [*CA* **82**, 12,5334 (1975)].

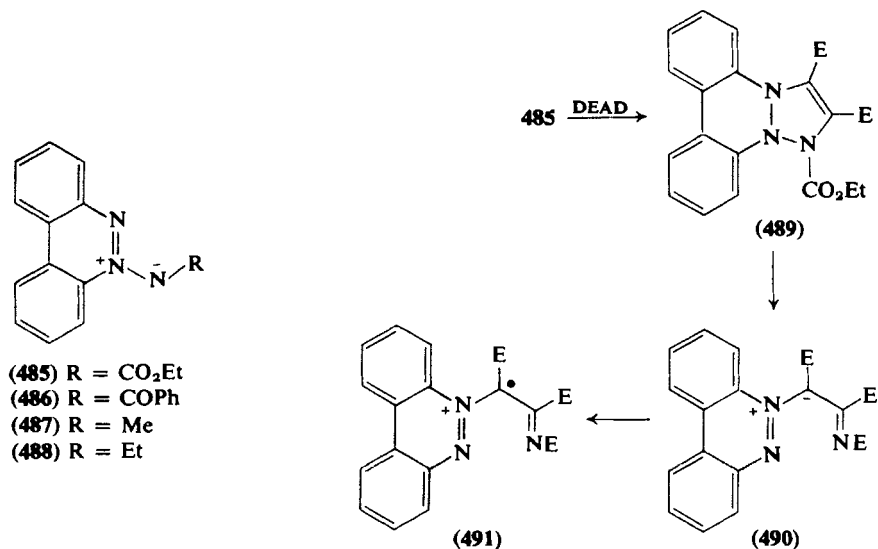
⁴⁵⁶ D. G. Farnum, R. J. Alaimo, and J. M. Dunston, *J. Org. Chem.* **32**, 1130 (1967).

⁴⁵⁷ S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 688 (1972); S. R. Challand, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 837 (1973).

⁴⁵⁸ S. R. Challand, S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 26 (1975).



DEAD exothermically in benzene or DMF to give initially **489**, which has three contiguous saturated nitrogen atoms and undergoes N—N bond fission to give the highly stabilized ylid **490**, which was isolated as the stable radical cation **491**. Analogous reactions with **486** were carried out.

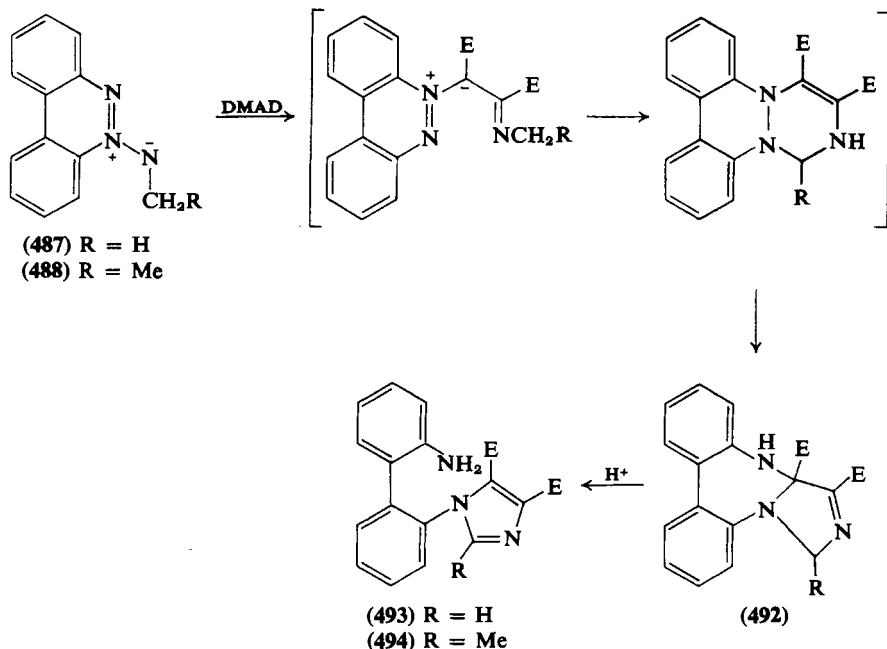


Anomalous cycloaddition reactions from benzocinnoline *N*-alkylimides and acetylenic esters were also described, in 1974, by Rees *et al.*⁴⁵⁹ Benzocinnoline *N*-alkylimides (**487** and **488**) gave adducts **492** via the sequence shown in Scheme 10; with acid, they rearranged to the imidazoles **493** and **494**.

Addition of acetylenic esters to **490** has been described⁴⁶⁰; DMAD gave the yellow **495** and a colorless compound, tentatively written as

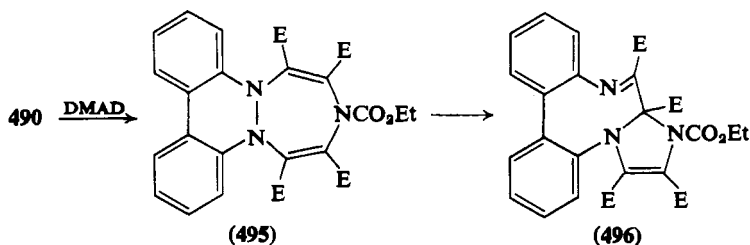
⁴⁵⁹ M. J. Rance, C. W. Rees, P. Stagnold, and R. C. Storr, *Chem. Commun.*, 658 (1974).

⁴⁶⁰ S. F. Gait, M. J. Rance, C. W. Rees, R. W. Stephenson, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 556 (1975).



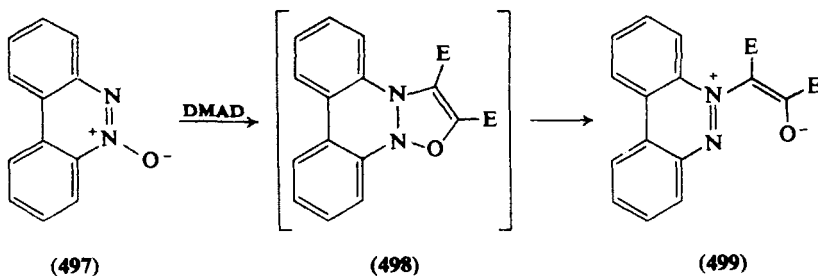
SCHEME 10

496. The former was slowly converted into the latter at room temperature, a reaction that proceeded rapidly on warming via a postulated diradical intermediate. When MP was added to **490** a compound corresponding to **495** was obtained, but no further rearrangement took place.



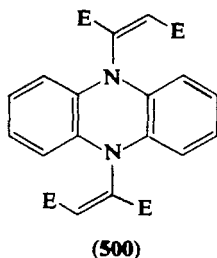
The reaction of benzocinnoline *N*-oxides (e.g., **497**) with excess DMAD for 3 hours at 190° gave low yields of the stable azomethine ylids **499**.⁴⁵⁷ The substrates added to the acetylene in a 1,3-dipolar fashion, a new reaction for azoxy compounds, and an electrocyclic

ring opening followed. Benz[*cd*]indazole *N*-oxide and 4,4-bis-(dimethylamino)azoxybenzene did not react under these conditions.



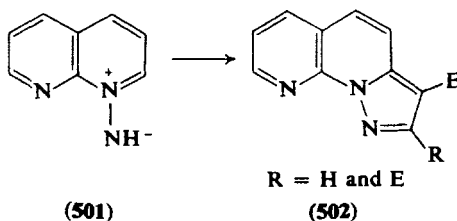
O. PHENAZINES

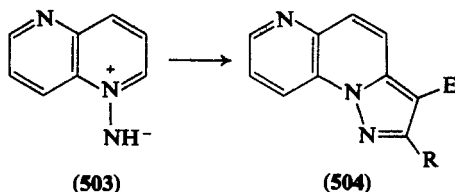
Phenazine in methanol, with DMAD, gives the dihydrophenazine 500, a reduction having taken place.³⁵¹



P. NAPHTHYRIDINES

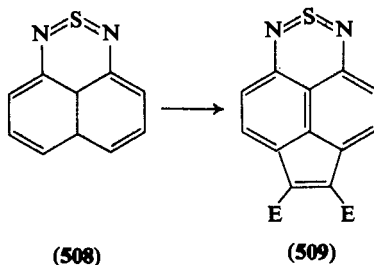
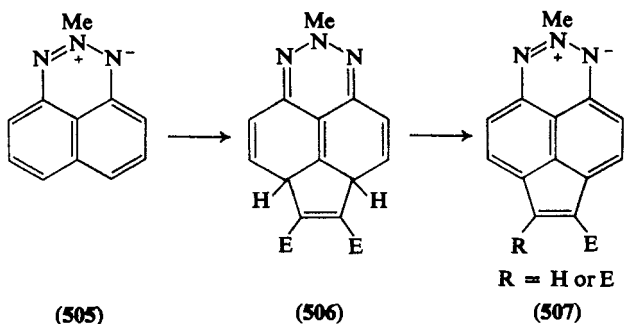
The reactions of *N*-imines of 1,5- and 1,8-naphthyridines with DMAD and MP proceed normally (501 \rightarrow 502; 503 \rightarrow 504).⁴²⁴





Q. NAPHTHOTRIAZINES

Rees *et al.*^{460,461} heated 2-methylnaphtho[1,8-*de*]triazine (505) with DMAD and EP in *o*-dichlorobenzene and obtained 30–40% of 2-methylacenaphtho[5,6-*de*]triazines (507). The reactions are cleaner in the presence of 3 equivalents of sulfur as a dehydrogenating agent; this must facilitate the transformation of 506 to 507. The product is a stable 14π aromatic system, possibly formed by a $1,11$ -dipolar ($12\pi + 2\pi$) cycloaddition. A similar reaction with the naphtho[1,8-*cd*]thiadiazine (508) and DMAD giving 509 was described.⁴⁶⁰

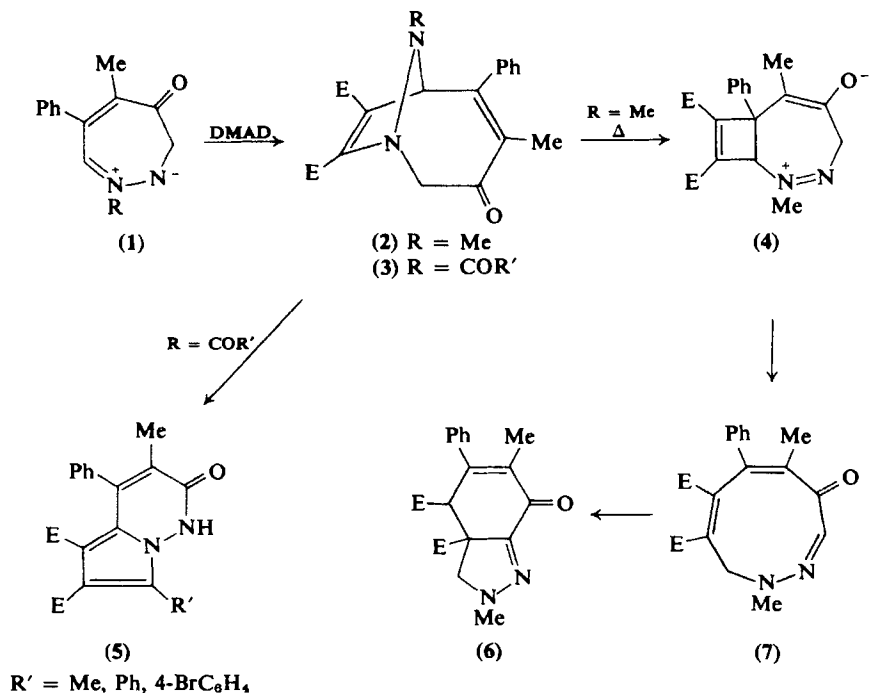


⁴⁶¹ C. W. Rees, R. W. Stephenson, and R. C. Storr, *Chem. Commun.*, 1281 (1972).

VI. Compounds from Seven-Membered Ring Heterocycles Containing Only Nitrogen as Heteroatom

A. 1,2-DIAZEPINES

Moore *et al.*⁴⁶² have studied cycloadditions to the 1,2-diazepinium betaines (1), which are also vinylogous azomethine imines. Ketenes and isocyanates add in a 1,5 manner and rearrange to 1,3-cycloadducts. Dimethyl acetylenedicarboxylate gave in 30 minutes 33% of 2, the formal product of a 1,3-cycloaddition, but possibly formed via a 1,5-cycloaddition. On heating, 2 gave 6 and another product via the postulated intermediates 4 and 7. Thermolysis of the related compounds 3⁴⁶³ gave 5.⁴⁶⁴

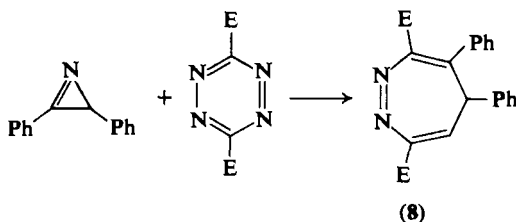


⁴⁶² O. S. Rothenberger, R. T. Taylor, D. L. Dalrymple, and J. A. Moore, *J. Org. Chem.* **37**, 2640 (1972).

⁴⁶³ J. A. Moore, R. C. Gearhart, O. S. Rothenberger, P. C. Thorstenson, and R. H. Wood, *J. Org. Chem.* **37**, 3774 (1972).

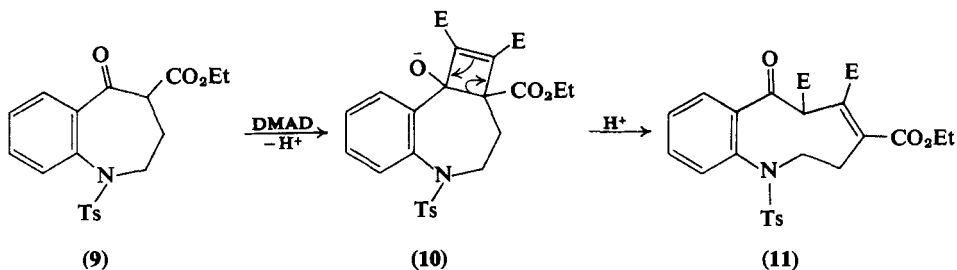
⁴⁶⁴ R. C. Gearhart, R. H. Wood, P. C. Thorstenson, and J. A. Moore, *J. Org. Chem.* **39**, 1007 (1974).

The diazepine **8** prepared as shown, gave no adduct with DMAD.⁴⁶⁵



B. BENZAZEPINONES

Proctor *et al.*⁴⁶⁶ treated the anion derived from **9** with DMAD in toluene at room temperature and isolated a high yield of the 1-benzazepin-7-one (**11**), which was probably formed via the unstable **10**.



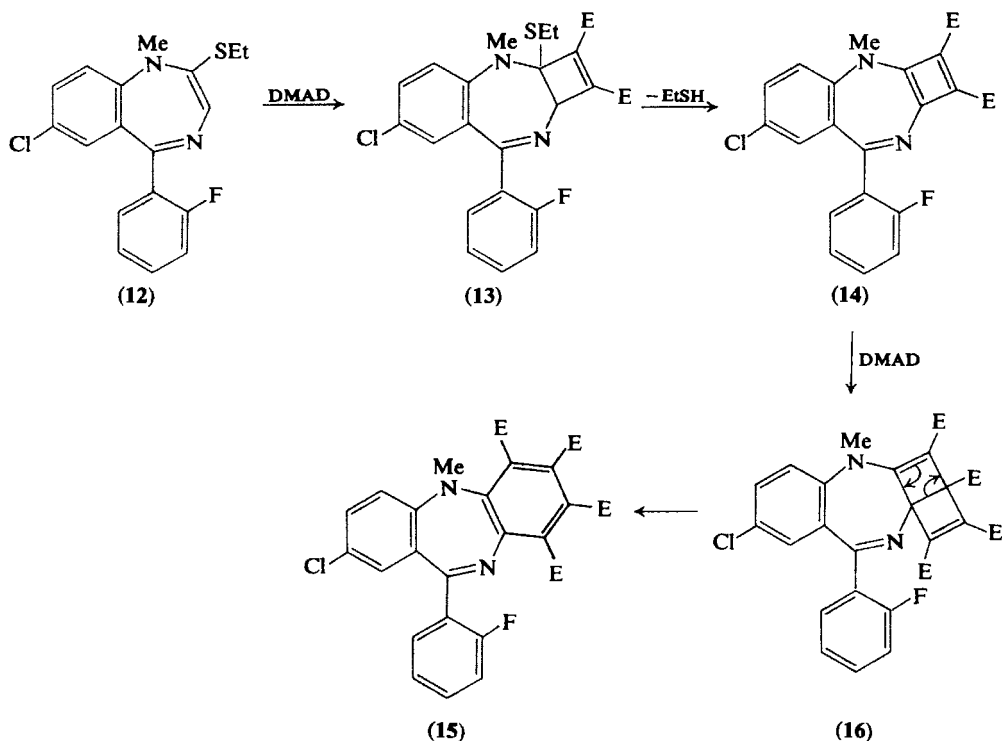
C. BENZODIAZEPINES

Additions of DMAD to the pharmacologically important benzodiazepines have been described by three different industrial research laboratories. Fryer *et al.*⁴⁶⁷ reacted **12** in hot dioxane and obtained 42% of **15**. Convincing structural evidence for the product was obtained from NMR. The authors suggested that the reaction proceeded normally to the cyclobutene **13** which then gave **14** by loss of ethanethiol; the latter could add a second mole of ester to give **16** which isomerized to **15** (Scheme 11); simpler schemes can also be devised.

⁴⁶⁵ G. C. Johnson and R. H. Levin, *Tetrahedron Lett.*, 2303 (1974).

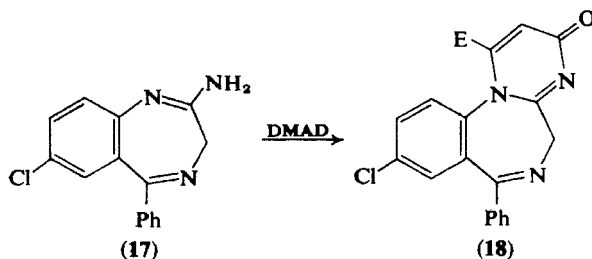
⁴⁶⁶ M. Lennon, A. McLean, I. McWatt, and G. R. Proctor, *J. Chem. Soc., Perkin Trans. 1*, 1828 (1974).

⁴⁶⁷ R. I. Fryer, D. L. Coffen, J. V. Earley, and A. Walser, *J. Heterocycl. Chem.* **10**, 473 (1973).



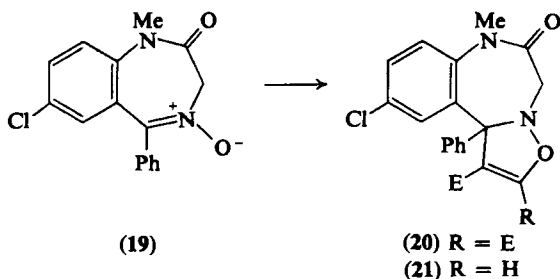
SCHEME 11

Addition of DMAD to the aminochlorobenzodiazepine **17** gave **18**; the addition of EP was also described. Cycloadditions of DMAD and EP to the *N*-oxide **19** gave **20** and **21**, respectively.^{468,469}



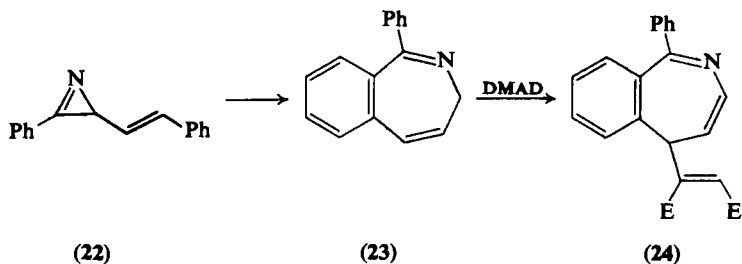
⁴⁶⁸ Sumitomo Co., Japanese Patent 74 93395 [*CA* **82**, 140,214 (1975)].

⁴⁶⁹ M. Raban, E. H. Carlson, J. Szmuszkovicz, G. Slomp, C. D. Chidester, and D. J. Duchamp, *Tetrahedron Lett.*, 139 (1975).



D. BENZAZEPINES

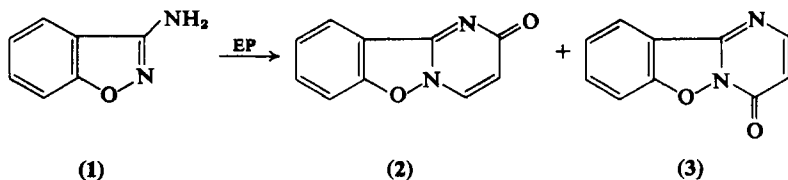
Padwa and Smolanoff⁴⁷⁰ irradiated *E* and *Z* 3-phenyl-2-styryl-2*H*-azirines (**22**) in benzene and isolated high yields of the benzazepine **23**; this with DMAD gave **24**.



VII. Compounds from Heterocycles Containing Both Nitrogen and Oxygen

A. BENZISOXAZOLES

Addition of propiolic esters to 3-aminobenzisoxazole (**1**) gave a mixture of **2** and **3**.⁴⁷¹

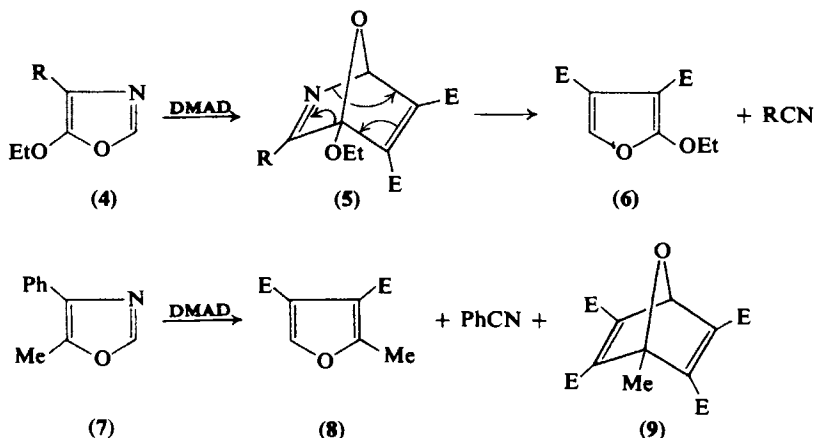


⁴⁷⁰ A. Padwa and J. Smolanoff, *Tetrahedron Lett.*, 33 (1974).

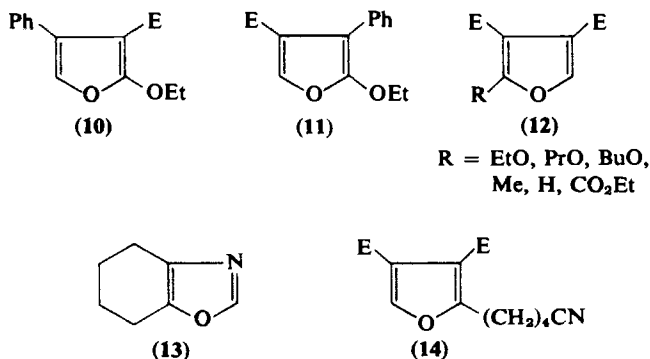
⁴⁷¹ H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **105**, 794 (1972).

B. OXAZOLES

Grigg *et al.*^{472,473} reported the first examples of the elimination of hydrogen cyanide and nitriles in retrocycloaddition reactions. The oxazoles **4** ($R = H$ or Me) with DMAD in cold ether led directly to the furan **6** and the appropriate nitrile; the expected intermediate **5** could not be isolated. The less reactive oxazole **7** was converted by DMAD into the furan **8** (69%) and benzonitrile only in boiling toluene; about 10%



of **9**, the Diels-Alder adduct of DMAD with the furan **8**, was also obtained. The oxazole **4** ($R = Me$) reacted only slowly with MPP in boiling toluene; the rate was increased by boron trifluoride and **10** and **11** resulted in 3:2 ratio.



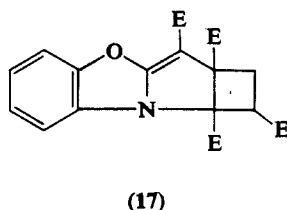
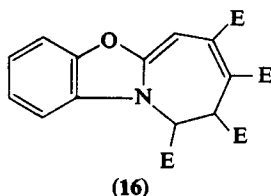
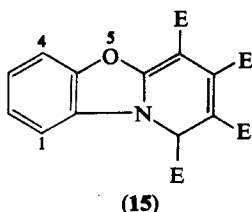
⁴⁷² R. Grigg, R. Hayes, and J. L. Jackson, *Chem. Commun.*, 1167 (1969).

⁴⁷³ R. Grigg and J. L. Jackson, *J. Chem. Soc.*, 552 (1970).

Substituted oxazoles heated with DMAD in toluene in the presence of hydroquinone gave⁴⁷⁴ the furans **12** in up to 90% yield. Dimethyl acetylenedicarboxylate reacts similarly with other oxazoles,⁴⁷⁵ whereas MP gives mixtures of the possible isomeric furans.⁴⁷⁶ Addition of DMAD to the oxazole **13** in boiling ether gave **14** with retention of the nitrile fragment.⁴⁷⁴

C. BENZOXAZOLES

Unlike oxazoles, benzoxazoles do not undergo Diels–Alder reactions with DMAD. Benzoxazole itself, without solvent, gives pyrido[2,1-*b*]-benzoxazole (**15**), the earlier⁴⁷⁷ 5*aH*-isomer structure being discarded⁴⁷⁸ because of the ¹³C NMR spectrum of the compound. 2-Methylbenzoxazole in acetonitrile gave on one occasion⁴⁷⁹ the azepine **16** and, on another,⁴⁸⁰ a compound that is almost certainly cyclobuta[4,5]pyrrolo-[2,1-*b*]benzoxazole (**17**).^{337,481}



Nair⁴⁸² reacted benzoxazole with a molar quantity of DMAD at room temperature for 10 days, then he heated the product for 6 hours at 100°, and obtained 3-methoxycarbonylmethylene-2-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (**18**), identical with that obtained from *o*-aminophenol and the acetylenic ester; his benzoxazole may have hydrolyzed before or during reaction.

⁴⁷⁴ G. Ya Kondrat'eva, L. B. Medvedskaya, and Z. N. Ivanova, *Iz. Akad. Nauk SSR, Ser. Khim.*, 2276 (1971) [*CA* 76, 59,332 (1972)].

⁴⁷⁵ T. Jaworski and T. Mijerski, *Rocz. Chem.* 50, 359 (1976).

⁴⁷⁶ J. J. K. Novak, *Coll. Czech. Chem. Commun.* 40, 2855 (1975).

⁴⁷⁷ R. M. Acheson, M. W. Foxton, and G. R. Miller, *J. Chem. Soc.*, 3200 (1965).

⁴⁷⁸ P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *J. Chem. Soc., Perkin Trans. I*, 1269 (1976).

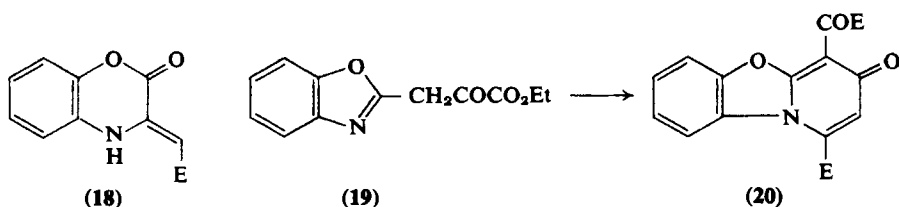
⁴⁷⁹ R. M. Acheson, M. W. Foxton, P. J. Abbott, and K. R. Mills, *J. Chem. Soc. C*, 882 (1967).

⁴⁸⁰ R. M. Acheson and W. R. Tully, *J. Chem. Soc. C*, 1623 (1968).

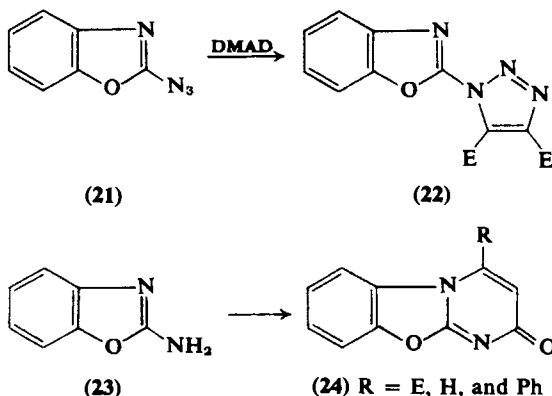
⁴⁸¹ R. M. Acheson and G. Procter, unpublished observations.

⁴⁸² M. D. Nair, *Indian J. Chem.* 7, 229 (1969).

The benzoxazole derivative **19**, with an activated methylene group, gave pyrido[2,1-*b*]benzoxazole (**20**) with DMAD,⁴⁸⁰ initial attack presumably having taken place on the nitrogen atom.



Addition of DMAD to substituted 2-azidobenzoxazoles (e.g., **21**) is stated⁴⁸³ to give triazoles (e.g., **22**), which are described as anthelmintics and nematocides. With 2-aminobenzoxazole (**23**), DMAD and other acetylenic esters are reported⁴⁸⁴ to give the products **24**, although isomeric structures seem equally possible.



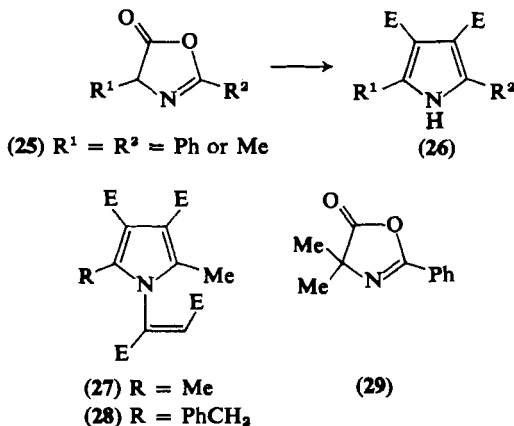
D. OXAZOLONES

Huisgen's group⁴⁸⁵ have described a new synthesis of pyrroles (**26**) from oxazol-5-ones (azlactones) (**25**) with DMAD and MP. The pyrrole derivatives formed *in situ* from 2,4-dimethyl- and 4-benzyl-2-methyloxazolone with DMAD underwent nucleophilic addition to a second mole of the acetylenic ester to give the Michael adducts **27** and **28**

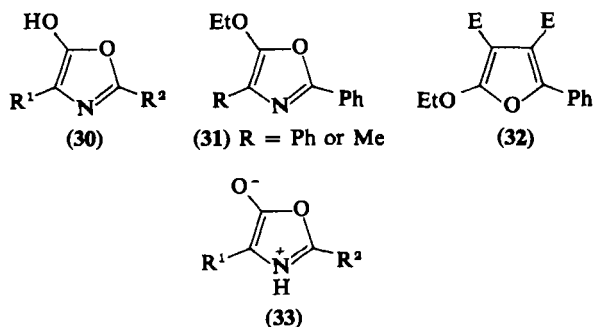
⁴⁸³ Ciba-Geigy A-G, German Patent 2,263,878 [CA 79, 78,815 (1973)].

⁴⁸⁴ H. Ogura, M. Kawano, and T. Itoh, *Chem. Pharm. Bull.* 21, 2019 (1973) [CA, 79, 137,078 (1973)].

⁴⁸⁵ R. Huisgen, H. Gotthardt, and H. O. Bayer, *Angew. Chem., Int. Ed. Engl.* 3, 135, 136 (1964).



respectively. The oxazolones (25) cannot be 1,3-dipoles so long as the 4-position retains its sp^3 character. The 4,4-disubstituted oxazolone 29 did not react with DMAD at 180° . 5-Hydroxyoxazoles (30) are not intermediates since 5-ethoxyoxazoles (31) react with DMAD by Diels-

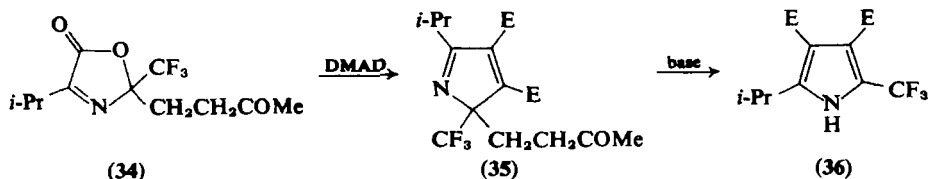


Alder addition to give nitriles and the furan 32. This suggests that the preliminary stage is tautomerization of the oxazolone and that an equilibrium concentration of the mesoionic tautomer 33 is essential for the 1,3-dipolar cycloaddition leading to pyrrole formation.^{486,487} Work complementary to that by Huisgen has been described by Steglich *et al.*,⁴⁸⁸ who found that heating 2*H*-oxazol-5-one (34) with DMAD at 210° gave the 2*H*-pyrrole 35, which was converted into 36 with base.

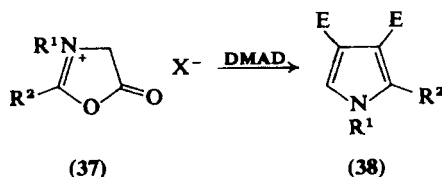
⁴⁸⁶ H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tetrahedron Lett.*, 487 (1964); H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.* 103, 2356 (1970).

⁴⁸⁷ H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.* 92, 4340 (1970).

⁴⁸⁸ W. Steglich, P. Gruber, H.-U. Heininger, and F. Kneidl, *Chem. Ber.* 104, 3816 (1971).

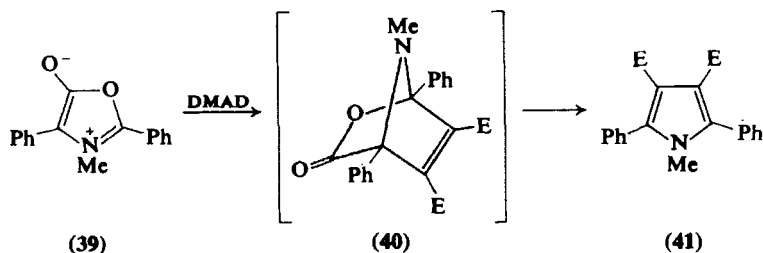


A brief report has described the addition of DMAD to the oxazolinium salts **37**, which also gave the pyrroles **38**.⁴⁸⁹



E. MESOIONIC OXAZOLONES

Huisgen and co-workers^{486,490} have described a useful synthesis of *N*-substituted pyrroles (**41**) from mesoionic oxazolones (**39**) via the intermediates **40**, which were not isolated. A variety of acetylenic esters (phenylpropionic, propionic, tetrolic, and DMAD) were used. The kinetics of these reactions have been studied.⁴⁹¹ The addition of carbon



disulfide to **39** gave **42**, which could be decomposed to the mesoionic thiazole **43**; the addition of DMAD to the latter gave the same thiophene (**44**)⁴⁹² as formed directly from DMAD and sulfur.

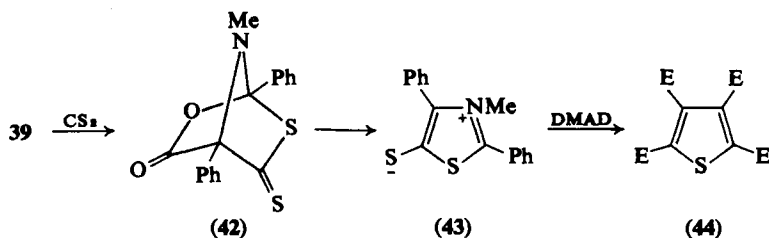
By varying the substituents attached to the mesoionic oxazolium

⁴⁸⁹ G. V. Boyd, *Jerusalem Symp. Quantum Chem. Biochem.*, p. 166 (1971) [*CA* **81**, 91,401 (1974)].

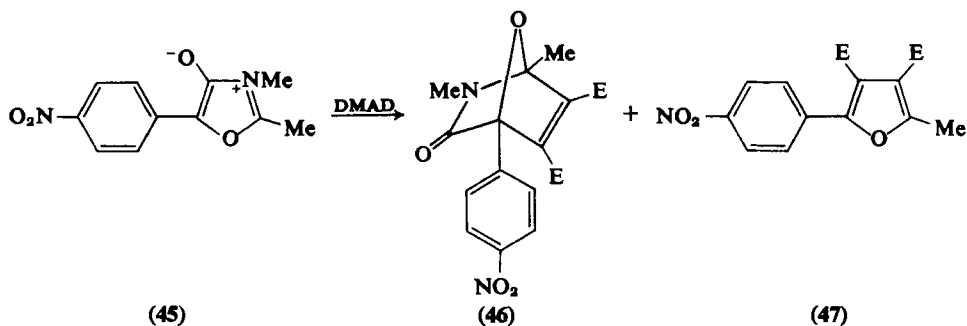
⁴⁹⁰ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.* **103**, 2611 (1970).

⁴⁹¹ R. Knorr, R. Huisgen, and G. K. Staudinger, *Chem. Ber.* **103**, 2639 (1970).

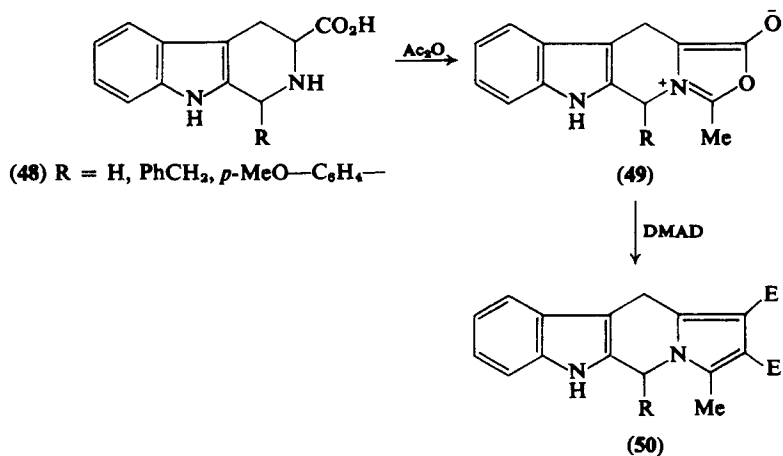
⁴⁹² E. Funke, R. Huisgen, and F. C. Schaefer, *Chem. Ber.* **104**, 1550 (1971).



ring, Japanese workers⁴⁹³ have been able to isolate the intermediate cycloadducts. Hence **45** with DMAD gave the adduct **46** and the furan **47**; heating the cycloadduct above 80° yielded **47** and methyl isocyanate. Other acetylenic dipolarophiles were also used.



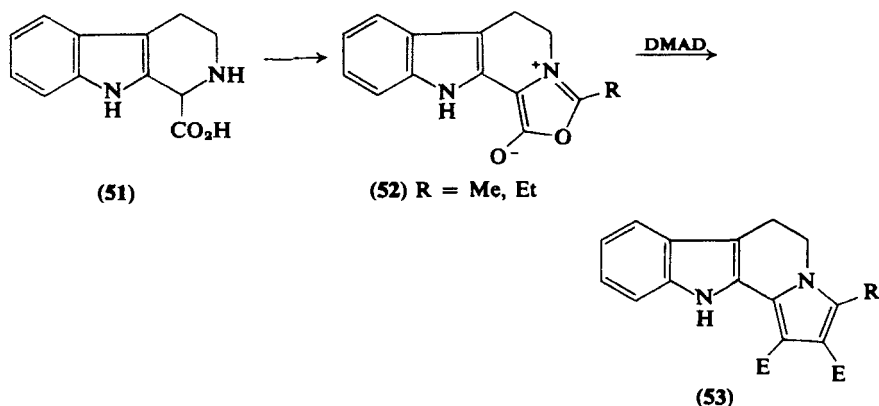
Hershenson⁴⁹⁴ found that the reaction of various tetrahydro- β -carboline-3-carboxylic acids (**48**) with DMAD in acetic anhydride



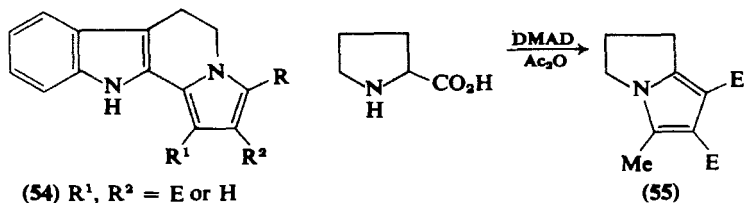
⁴⁹³ T. Ibata, M. Hamaguchi, and H. Kiyohara, *Chem. Lett.* 1, 21 (1975).

⁴⁹⁴ F. M. Hershenson, *J. Org. Chem.* 37, 3111 (1972).

directly afforded the corresponding indolizino[6,7-*b*]indoles (50) in moderate yields. Initial formation of the mesoionic oxazole 49 was proposed, and formation of an unstable cycloadduct followed by loss of carbon dioxide could give the products. In a similar manner, treatment of β -carboline-1-carboxylic acid (51) in various anhydrides with a variety of acetylenic dipolarophiles furnished the corresponding indolizino[8,7-*b*]indoles. For example, 51 with DMAD and acetic and propionic anhydrides gave 53, but the corresponding derivative from



trifluoroacetic anhydride could not be made. Isomeric compounds (54) were made from EP. Likewise, L-proline gave the pyrrolizine 55.⁴⁹⁰



F. REISSERT COMPOUNDS

The mechanism proposed⁴⁹⁵⁻⁴⁹⁷ for the acid-catalyzed hydrolysis of Reissert compounds (1-acyl-1,2-dihydro-2-cyanoquinolines or 2-acyl-1,2-dihydro-1-cyanoisoquinolines) invokes a mesoionic oxazolinium

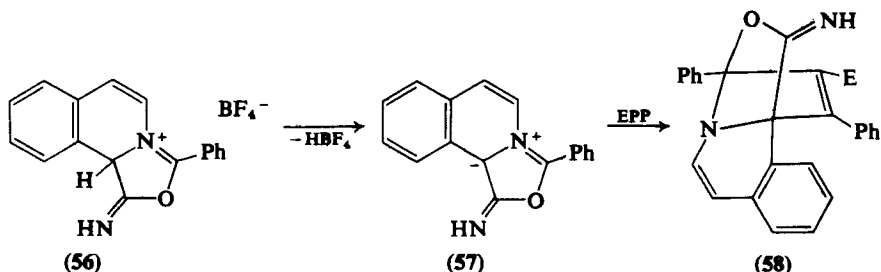
⁴⁹⁵ W. E. McEwen, I. C. Mineo, Y. H. Shen, and G. Y. Han, *Tetrahedron Lett.*, 5157 (1968).

⁴⁹⁶ R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.* 77, 5042 (1955).

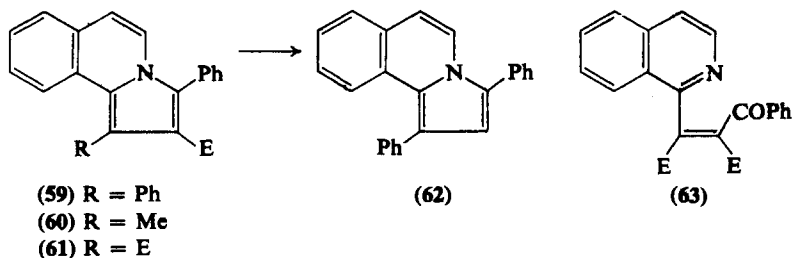
⁴⁹⁷ E. K. Evangelidou and W. E. McEwen, *J. Org. Chem.* 31, 4110 (1966).

imine; such an intermediate can be captured by 1,3-dipolar cycloaddition with acetylenic and other dipolarophiles.⁴⁹⁸

2-Benzoyl-1,2-dihydro-1-cyanoisoquinoline was treated with fluoroboric acid in glacial acetic acid to give the Reissert salt **56**; reactions of the latter with EPP, DMAD, and ethyl tetrolate were examined. With EPP, the initial bridged compound **58** was isolated as a moderately stable crystalline compound, and was the first example of an isolated



intermediate from all the known 1,3-dipolar addition reactions of the same general type, involving mesoionic oxazolones, 1,2,3-oxadiazolones (sydnones), and 5-imino-1,2,3-oxadiazoles (sydnone imines). In addition to the primary adduct **58**, its decomposition product (**59**) was isolated when EPP was used in boiling methylene chloride:ethanol.⁴⁹⁸ Pyrolysis of **58** for 30 minutes at 220° gave 65% of **59**. Compound **59** was hydrolyzed and decarboxylated to **62**, which was unambiguously synthesized.



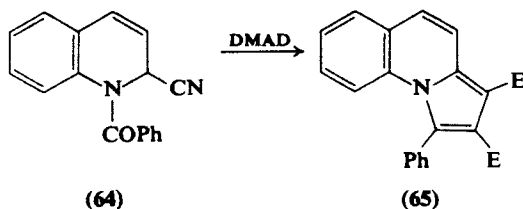
Factors influencing orientation in the condensation of **57** with dipolarophiles were examined by employing ethyl tetrolate in place of the phenylpropiolate. A clean reaction was not obtained, but eventually **60** was isolated indicating that the sterically less demanding ester still adds in the same manner.

Condensation of **56** with DMAD was successful, and 90% of **61** was isolated; no product corresponding to **58** was observed. Reaction of the

⁴⁹⁸ W. E. McEwen, I. C. Mineo, and Y. H. Shen, *J. Am. Chem. Soc.* **93**, 4479 (1971).

lithium salt of 2-benzoyl-1,2-dihydro-1-cyanoisoquinoline with DMAD gave **63** which was converted into **61** with polyphosphoric acid at 120°.

Reactions of quinoline Reissert compounds were less satisfactory than those of the corresponding isoquinolines. The hydrochloride of **64** with DMAD gave **65** in only 7% yield in methylene chloride:ethanol, and 10% in DMF. From a study of the mechanism of the 1,3-dipolar addition of Reissert salts to arylpropiolate esters, McEwen *et al.*⁴⁹⁹ concluded that a concerted cyclization was more probable than a two-step process.

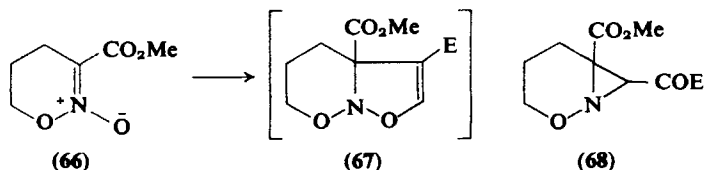


G. MORPHOLINE

The Michael-type addition of morpholine to propiolic, tetrolic, phenylpropionic, and acetylenedicarboxylic esters has been described by Postovskii *et al.*⁵⁰⁰

H. OXAZINES

Chlenov *et al.*⁵⁰¹ reacted 3-methoxycarbonyl-4,5-dihydro-6*H*-1,2-oxazine *N*-oxide (**66**) with excess MP for 24 hours at room temperature and obtained 92% of the interesting aziridine derivative **68**; the authors postulate the 4-isoxazoline intermediate **67**. A similar reaction between nitrooxazine *N*-oxide (**69**) and EP and MP gave a high yield of the



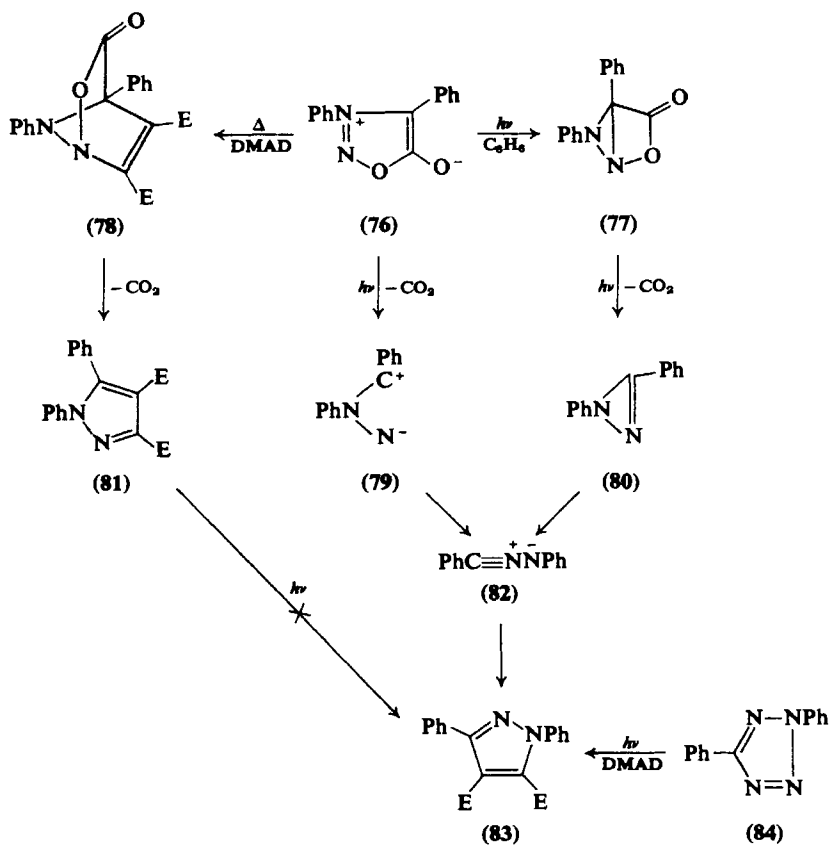
⁴⁹⁹ W. E. McEwen, K. B. Kanitkar, and W. M. Hung, *J. Am. Chem. Soc.* **93**, 4484 (1971).

⁵⁰⁰ I. Ya. Postovskii, E. I. Grinblat, and L. F. Treflova, *Zh. Obshch. Khim.* **31**, 400 (1961) [*CA* **55**, 23,541 (1961)].

⁵⁰¹ I. E. Chlenov, I. L. Sokolova, S. S. Novikov, and V. A. Tartakovskii, *Izv. Akad. Nauk SSR, Ser. Khim.*, 473 (1973) [*CA* **79**, 5304 (1973)].

The reactions of sydnone with acetylenic esters are generally thermally induced concerted processes which are allowed on orbital symmetry considerations.⁸ On the basis of Huisgen's mechanistic study,⁵⁰⁵ the conversion of **71** into **73** proceeds through the formation of **72** in a slow rate-determining step, followed by rapid loss of carbon dioxide, giving the pyrazole **73**.

Irradiation of diphenylsydnone (**76**) with DMAD in benzene gave 67% of the pyrazole **83**, which is different from the pyrazole **81** formed under thermal conditions.⁵⁰⁷ The authors showed that it was not



SCHEME 12

⁵⁰⁵ R. Huisgen and H. Gotthardt, *Chem. Ber.* **101**, 1059 (1968).

⁵⁰⁶ K. T. Potts and U. P. Singh, *Chem. Commun.*, 66 (1969).

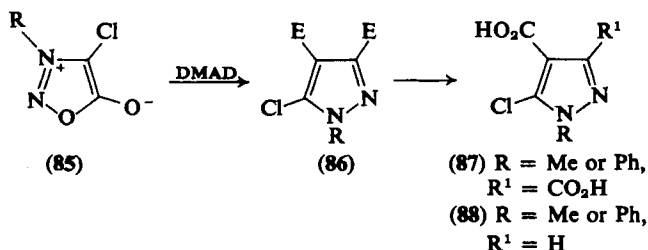
⁵⁰⁷ C. S. Angadiyavar and M. V. George, *J. Org. Chem.* **36**, 1589 (1971).

possible to photoisomerize (81) to (83). A plausible route for the formation of **83** is shown in Scheme 12; the assumption was made that sydnone (**76**) was first converted photochemically into the intermediate **77**, a structure which was originally proposed for sydnones by Earl and Mackney⁵⁰⁸ in 1935. Loss of carbon dioxide from **77** gave the diazirine **80**, which was then ring-opened to the nitrile imine **82**. Alternatively, **76** could lose carbon dioxide under photolytic conditions giving the nitrene: carbene (**79**) which would rearrange to **82**. Addition of acetylenic esters to the nitrile imine through a photochemical or thermal pathway would then give the pyrazole **83**.

Photolysis of 2,5-diphenyltetrazole (**84**) in the presence of DMAD gave 81% of the pyrazole **83**,⁵⁰⁷ and the nitrilimine **82** is again implicated as an intermediate.

Almost simultaneously, papers by Schmid *et al.*⁵⁰⁹ and by Gotthardt and Reiter⁵¹⁰ appeared on the photoaddition of DMAD to sydnones; the last authors also used propiolic and phenylpropiolic esters. Ohta *et al.*⁵¹¹ showed that similar reactions could be carried out with 3-alkyl-4-phenylsydnones, and other papers on the addition of acetylenic esters to sydnones have appeared.⁵¹²⁻⁵¹⁴

Thermal addition of DMAD to 4-halosydnone (**85**) gave **86**, which was hydrolyzed to **87** and **88**, halogen being retained.⁵¹⁵



Irradiation⁵¹⁶ of 3,4-diphenylsydnone acetimine (**89**) gave 11% of anhydro-3-acetyl-4-hydroxy-1,5-diphenyl-1,2,3-triazolium hydroxide (**92**) and 10% of 4-hydroxy-1,5-diphenyl-1,2,3-triazole (**91**). Irradiation

⁵⁰⁸ J. C. Earl and A. W. Mackney, *J. Chem. Soc.*, 899 (1935).

⁵⁰⁹ M. Marky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 1275 (1971).

⁵¹⁰ H. Gotthardt and F. Reiter, *Tetrahedron Lett.*, 2749 (1971).

⁵¹¹ Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jpn.* **45**, 3202 (1972).

⁵¹² B. V. Badami and G. S. Puranik, *Indian J. Chem.* **12**, 671 (1974); [*CA*, **82**, 31,293 (1975)].

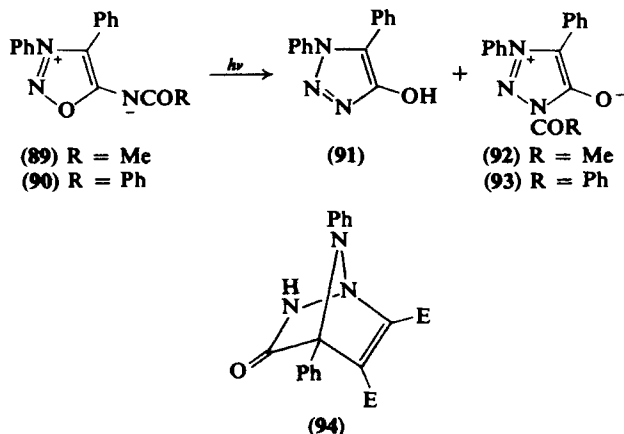
⁵¹³ B. V. Badami and G. S. Puranik, *Can. J. Chem.* **53**, 913 (1975).

⁵¹⁴ B. V. Badami and G. S. Puranik, *Rev. Roum. Chim.* **20**, 981 (1975).

⁵¹⁵ H. Dickopp, *Chem. Ber.* **107**, 3036 (1974).

⁵¹⁶ A. Chinone and M. Ohta, *Chem. Lett.*, 969 (1972) [*CA* **78**, 15,224 (1973)].

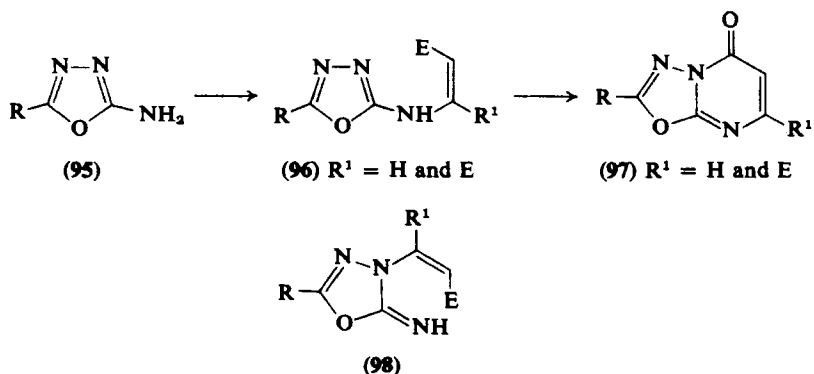
of the phenyl analog **90** under the same conditions afforded 35% of **91** and 2% of **93**. The photochemical reactions of sydnone in the presence



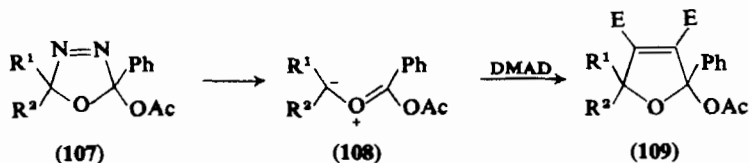
of DMAD, as described in the foregoing, afforded the addition products of nitrile imines. However, irradiation of **89** in DMAD gave **91**, **92**, and an adduct whose structure is probably **94**.⁵¹⁶

J. 1,3,4-OXADIAZOLES

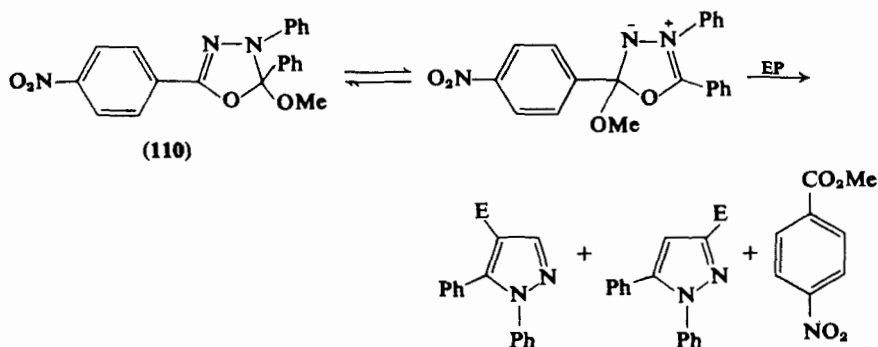
The addition of DMAD, DEAD, and propiolic ester to 2-amino-1,3,4-oxadiazoles (**95**) led to the Michael adducts **96**, which were cyclized to 5-oxo-1,3,4-oxadiazolo[3,2-*a*]pyrimidines (**97**). The alternative mode of addition leading to **98** was not observed. The structures were assigned spectroscopically.⁵¹⁷



⁵¹⁷ P. Henklein, G. Westphal, and R. Kraft, *Tetrahedron* **29**, 2937 (1973).

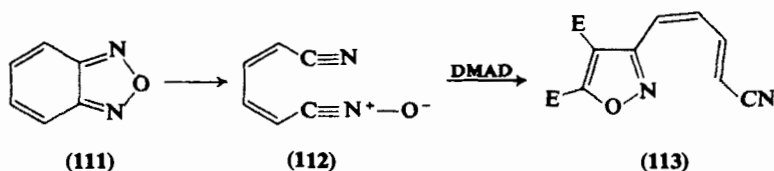


DMAD, giving **109**. Trapping of a similar intermediate derived from methoxyoxadiazoline (**110**) with EP has been described.⁵²²



M. BENZOFURAZANS

The photoreaction of benzfuran (111) and DMAD gives isoxazoles (113).⁵²³ Ring cleavage to **112** was postulated, this intermediate being trapped with DMAD to form the geometrical isomers of **113**.



N. 1,3,4-OXADIAZINES

Freeman *et al.*⁵²⁴ have shown that 1,3,4-oxadiazin-6-one 4-oxides (**114**)⁵²⁵ react with a variety of acetylenes to produce acylbutenolides

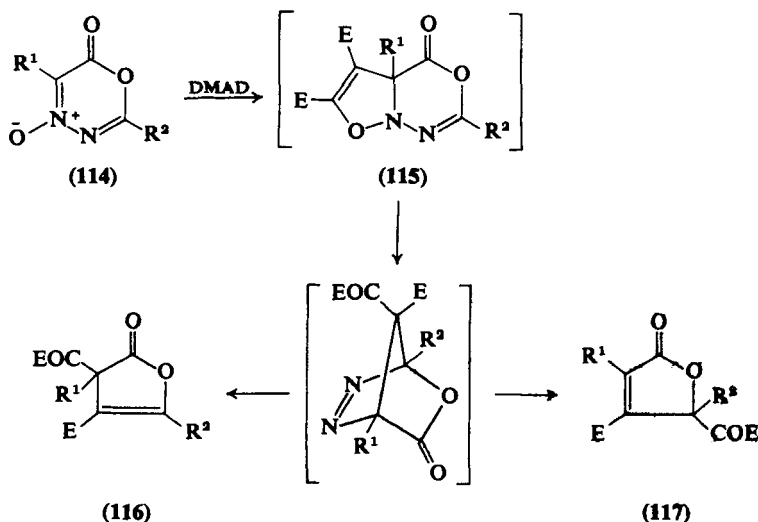
⁵²² G. Scherowsky and H. Franke, *Tetrahedron Lett.*, 1673 (1974).

⁵²³ I. Yavari, S. Esfandiari, A. J. Mostashari, and P. W. W. Hunter, *J. Org. Chem.* **40**, 2880 (1975).

⁵²⁴ J. P. Freeman, J. A. Kassner, and R. C. Grabiak, *J. Org. Chem.* **40**, 3402 (1975).

⁵²⁵ J. P. Freeman, D. L. Surbey, and J. A. Kassner, *Tetrahedron Lett.*, 3797 (1970).

(116 and 117), the structure of the products being dependent on the nature of the substituents on the heterocycle and the acetylene. The mechanism for the transformation involves a rearrangement of the primary cycloadduct, a fused Δ^4 -isoxazoline (115), which is thermally labile and rearranges in a fashion analogous to the Cope rearrangement of 1,5-dienes. Products 116 and 117 then result from loss of nitrogen and the migration of the acyl group to either of the two carbons formerly attached to nitrogen in 114.



VIII. Compounds from Heterocycles Containing Nitrogen, Oxygen, and Phosphorus

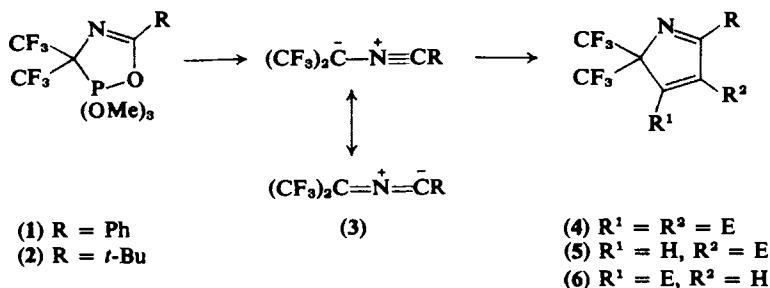
A. OXAZAPHOSPHOLES

4,5-Dihydro-1,3,5-oxazaphospholes (1 and 2) react with alkynes at temperatures between 100° and 140°C in toluene or xylene.⁵²⁶ Phosphate esters are eliminated and 1:1 adducts (4) of the resulting nitrogen ylids (3) are obtained.⁵²⁷ Similar reactions with MP have been described and the ratio of adducts 5 and 6 studied⁵²⁷; with 1 the ratio was 78:22, whereas 2 gave 70:30. The photoaddition of 1 to DMAD was carried out and 4 was again obtained.⁵²⁸

⁵²⁶ K. Burger, J. Fehn, and E. Moll, *Chem. Ber.* **104**, 1826 (1971).

⁵²⁷ K. Burger and J. Fehn, *Angew. Chem., Int. Ed. Engl.* **10**, 728,729 (1971).

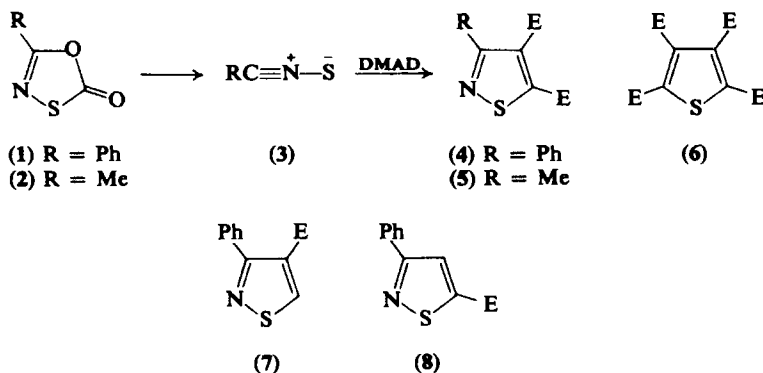
⁵²⁸ K. Burger and J. Fehn, *Tetrahedron Lett.*, 1263 (1972); *Chem. Ber.* **105**, 3814 (1972).



IX. Compounds from Heterocycles Containing Nitrogen, Oxygen, and Sulfur

A. 1,3,4-OXATHIAZOLES

Franz and Black⁵²⁹ have studied the thermolysis and photolysis of 1,3,4-oxathiazol-2-one (1).⁵³⁰ This compound is thermally labile and yields benzonitrile and sulfur instead of the expected phenyl isocyanate and carbonyl sulfide. It is probable that benzonitrile sulfide (3) is an intermediate and this appears to be confirmed by formation of the adduct 4 in 90% yield when 1 is heated with 2 moles of DMAD at 130° in chlorobenzene. Heating a mixture of benzonitrile and sulfur with DMAD gave tetramethyl thiophenetetracarboxylate (6), also obtained without the nitrile. The formation of the isomeric isothiazoles 7 and 8 from 1 and EP⁵³¹ is similar to the production of the corresponding



⁵²⁹ J. E. Franz and L. L. Black, *Tetrahedron Lett.*, 1381 (1970).

⁵³⁰ A. Senning, *Acta Chem. Scand.* **21**, 1871 (1967).

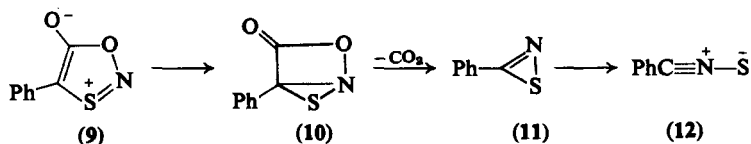
⁵³¹ R. Huisgen, *J. Org. Chem.* **33**, 2291 (1968).

oxazoles from benzonitrile oxide and propiolic ester. In this case the reaction via the sulfide or an intermediate complex⁵³² could equally well explain the results. Kinetic studies⁵³³ have provided support for benzonitrile sulfide (3) as an intermediate in the thermolysis of 1; the 5-methyl derivative 2 gave 5, presumably via acetonitrile sulfide.

Dimethyl 3-phenylisothiazole-4,5-dicarboxylate (4) has been claimed to be an effective broad-leaf post-emergent herbicide.⁵³⁴

B. MESOIONIC 1,3,2-OXATHIAZOLES

Gotthardt⁵³⁵ photolyzed solutions of 4-aryl-1,3,2-oxathiazolium-5-oxide (9)⁵³⁶ and postulated the formation of benzonitrile sulfide (12) via the interesting intermediates 10 and 11; sulfide 12 was trapped with DMAD and EP as described above, yielding 6, 7, and 8. The photolysis of 9 in neat DMAD gives identical results.⁵³⁷



X. Compounds from Heterocycles Containing Nitrogen and Sulfur

A. ISOTHIAZOLES

Isothiazoline-5-thiones (1 and 2; cf. 12, Section IX) formed adducts 3 and 4 on brief warming in benzene with one molecule of DMAD.⁵³⁸ The isomeric isothiazoline-3-thione (6) reacted more slowly (refluxing 24 hours in benzene) to form the 1:2-molar adduct 7. Adduct 3 formed 5 after refluxing with DMAD in wet (?) benzene for a further 48 hours, but adduct 4 was stable under these conditions.

Addition of hydroxyisothiazoles to MP is described in a patent.⁵³⁹

⁵³² R. Huisgen, H. Gotthardt, and R. Grashey, *Angew. Chem., Int. Ed. Engl.* **1**, 48 (1962).

⁵³³ R. K. Howe and J. E. Franz, *Chem. Commun.*, 524 (1973).

⁵³⁴ J. E. Franz, U.S. Patent 3,699,155 [CA 78, 29,759 (1973)].

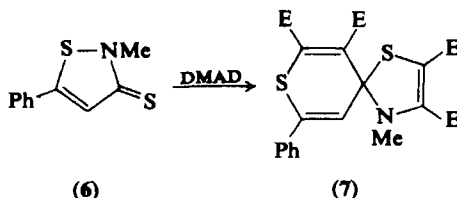
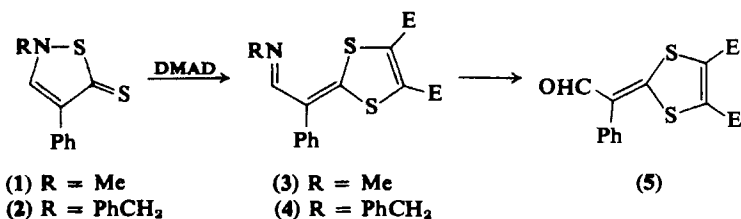
⁵³⁵ H. Gotthardt, *Tetrahedron Lett.*, 1277 (1971).

⁵³⁶ H. Gotthardt, *Chem. Ber.* **105**, 188, 196 (1972).

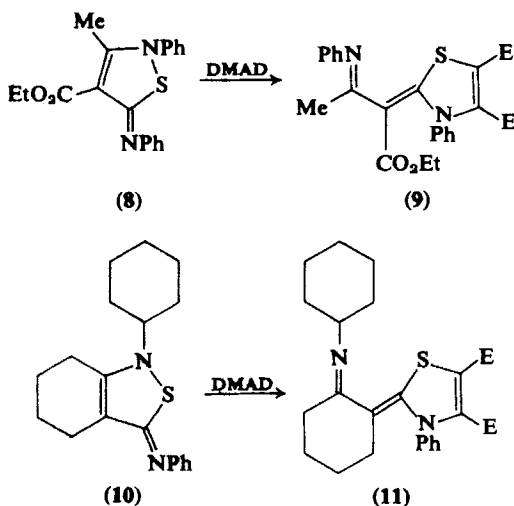
⁵³⁷ N. Harrit, K. Bechgaard, O. Buchardt, and S. Harnung, *Chem. Commun.*, 1125 (1972).

⁵³⁸ M. S. Chauhan, M. E. Hassan, and D. M. McKinnon, *Can. J. Chem.* **52**, 1738 (1974).

⁵³⁹ S. N. Lewis and G. A. Miller, U.S. Patent 3,835,150 [CA 81, 104,454 (1974)].



Behringer *et al.*⁵⁴⁰ added DMAD to the isothiazolinimines 8 and 10 to give 9 and 11, respectively.



B. THIAZOLES, BENZOTHAZOLES, AND THEIR ALKYL DERIVATIVES

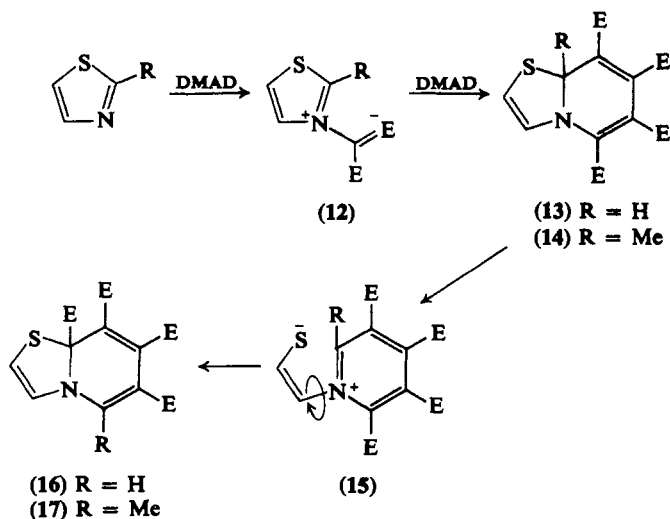
The products from thiazole, and a number of derivatives, with DMAD were examined in 1964 by two research groups^{541,542}; their conclusions

⁵⁴⁰ H. Behringer, J. Kilger, and R. Wiedenmann, *Tetrahedron Lett.*, 1185 (1968).

⁵⁴¹ R. M. Acheson, M. W. Foxton, and G. R. Miller, *J. Chem. Soc.*, 3200 (1965).

⁵⁴² D. H. Reid, F. S. Skeleton, and W. Bonthron, *Tetrahedron Lett.*, 1797 (1964).

have been recently corrected.⁵⁴³ Initial reaction (Scheme 13) in dimethylformamide takes place at the nitrogen atom and presumably 1:2-molar adducts, such as **13** are formed. Ring-opening to **15**, followed by cyclization in the alternative mode, or a [1,5] sigmatropic shift of the sulfur atom to give an equivalent result, now occurs to yield **16**. In the



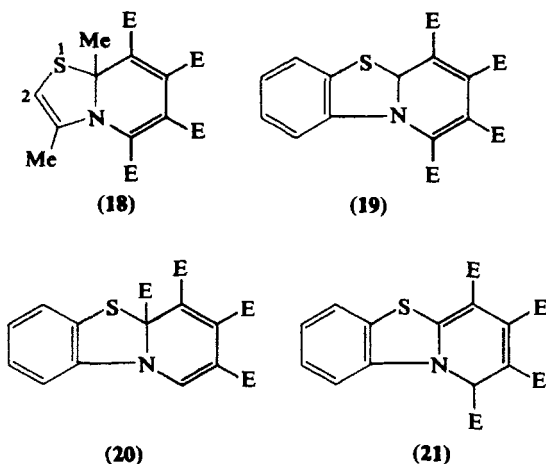
SCHEME 13

case of 2-methylthiazole the structure of adduct **17** has been determined by X-ray methods.⁵⁴³ Similar rearrangements take place in reactions involving 4- and 5-methyl- and 2,5-dimethylthiazole and benzothiazole, giving **20**. However, X-ray studies⁵⁴³ show that the product from 2,4-dimethylthiazole is formed without rearrangement, has structure **18**, and is stable at 150° in 1,2-dichlorobenzene. The relative stability of **18**, compared with its analogs which rearrange, can be associated with increased steric hindrance to the formation and rotation of the ring-opened intermediate (cf. **15**) or to the [1,5] shift. In the case of thiazole, unsuccessful attempts were made⁵⁴⁴ to detect **13** or other possible intermediates (cf. **12**) by carrying out the reaction using fully deuteriated dimethylformamide as solvent in an NMR spectrometer. As the temperature was raised slowly from -40° to +34°, the reaction started at ca. +5°, but only starting materials and the rearranged adduct **16** could be observed. A minor product in the case of benzothiazole

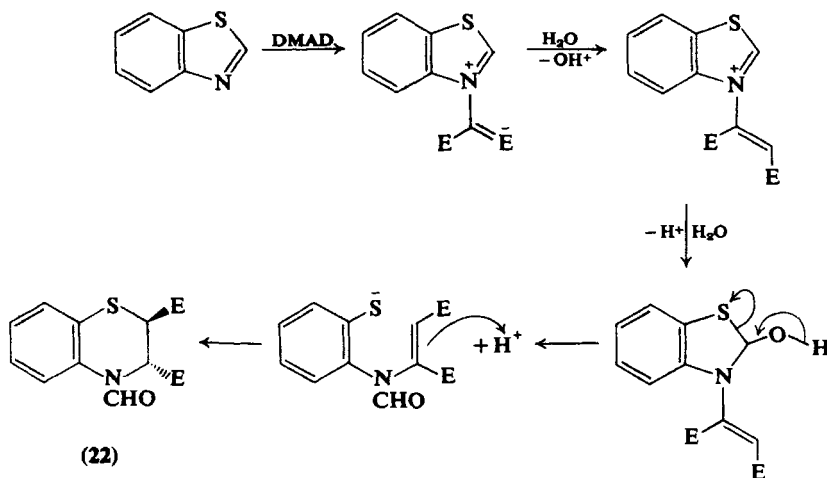
⁵⁴³ P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *Chem. Commun.*, 155 (1975); *J. Chem. Soc., Perkin Trans. I*, 1269 (1976).

⁵⁴⁴ R. M. Acheson, *Khim. Geterotsikl. Soedin.*, 1011 (1976).

(which became the main product using methanol as solvent) is **21**, whose structure was established by X-ray diffraction.⁵⁴⁵ This compound



is clearly formed from the same intermediate (19) which leads to **20** but by a competing [1,5] hydrogen shift. Another compound (**22**) formed from benzothiazole and identified by X-ray crystallography has been associated with the presence of water in the reaction medium (Scheme

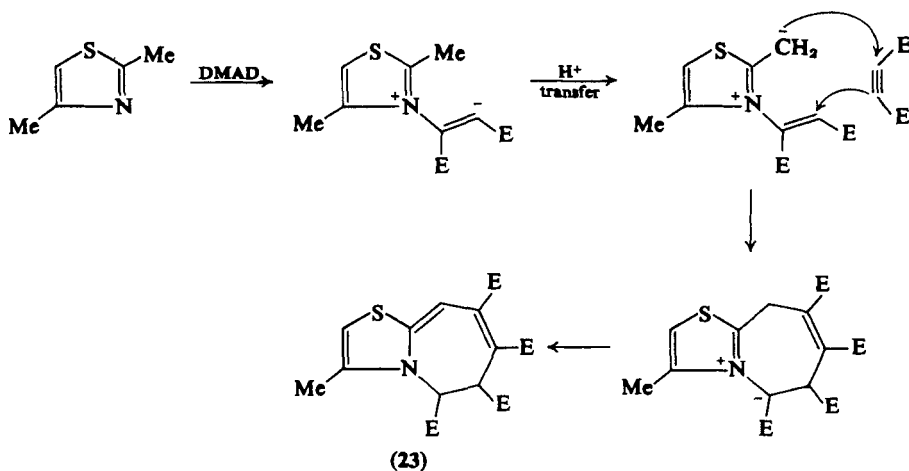


SCHEME 14

⁵⁴⁵ H. Ogura, K. Kikuchi, H. Takayanagi, K. Furuhashi, and Y. Iitaka, *Chem. Commun.*, 759 (1974).

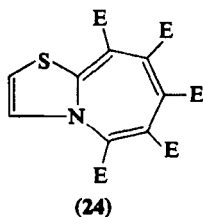
14),⁵⁴⁶ and can be obtained in high yield when the correct molar proportions are used.^{547,548}

The effect of solvent on these types of reaction is particularly well illustrated by the case of 2,4-dimethylthiazole: in dimethylformamide, **18** is obtained; in acetonitrile or dimethyl sulfoxide, a mixture of **18** and **23** results and using tetrahydrofuran, dichloromethane, or nitromethane, essentially only **23** is produced^{541,544} Adduct **23** could be formed as outlined in Scheme 15, and similar compounds are obtained from 2-ethylthiazole, suitably substituted benzothiazoles⁵⁴¹ and some other heterocycles.



SCHEME 15

A minor product from thiazole and DMAD is **24**.⁵⁴¹



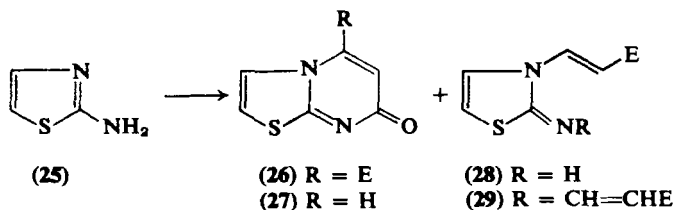
⁵⁴⁶ H. Ogura, K. Kikuchi, H. Takayanagi, K. Furuhashi, I. Iitaka, and R. M. Acheson, *J. Chem. Soc., Perkin Trans. 1*, 2316 (1975).

⁵⁴⁷ A. McKillop and T. S. B. Sayer, *Tetrahedron Lett.*, 3081 (1975).

⁵⁴⁸ A. McKillop, T. S. B. Sayer, and G. C. A. Bellinger, *J. Org. Chem.* **41**, 1328 (1976).

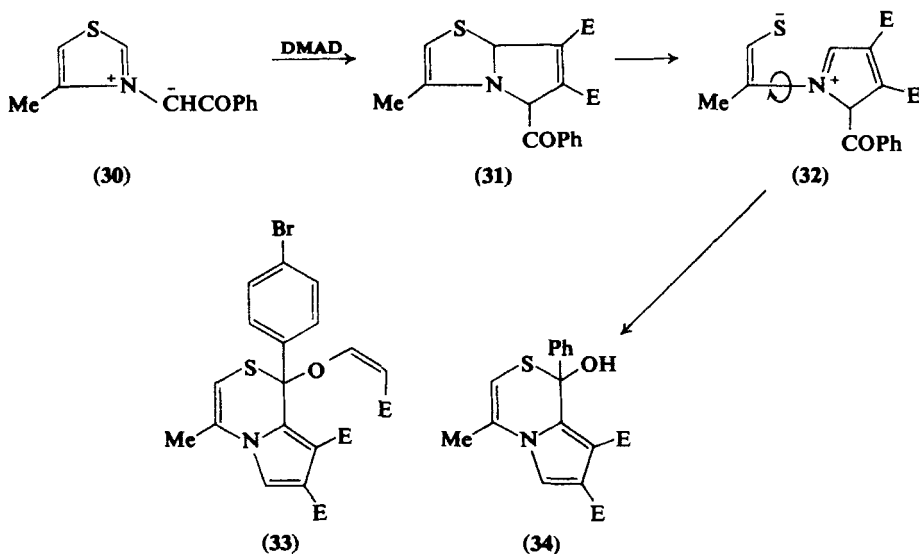
C. FUNCTIONALLY SUBSTITUTED THIAZOLES

The addition of DMAD to 2-aminothiazole (25) gave 26, whereas propiolic ester gave 27, 28 and 29, all derived by Michael-type additions.⁵⁴⁹ Dunwell and Evans^{550,551} have also added acetylenic esters to 2-amino- (and 2-amino-4-methyl)thiazole and obtained 26 and 27 from DMAD and EP, and similar compounds from tetrolic and phenyl-propionic esters. By independent synthesis, these compounds were shown not to have the isomeric structures derived by initial addition to the exocyclic nitrogen.



D. THIAZOLIUM YLIDS

Thiazolium ylids (e.g., 30) undergo initial reaction with DMAD and dibenzoylacetylene in the expected way to give structures such as 31, but



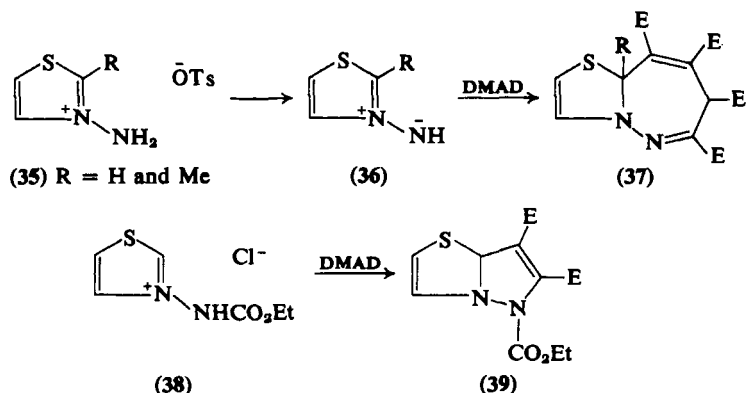
⁵⁴⁹ H. Reimlinger, *Chem. Ber.* 104, 2232 (1971).

⁵⁵⁰ D. W. Dunwell and D. Evans, *J. Chem. Soc. C*, 2094 (1971).

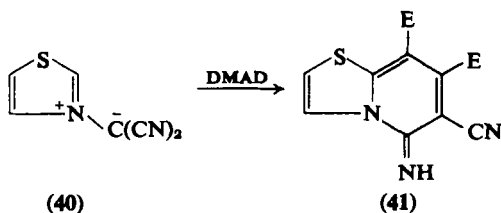
⁵⁵¹ D. Evans, U.K. Patent 1,345,148 [CA 80, 133,418 (1974)].

then an interesting rearrangement occurs.⁵⁵² The thiazoline ring opens, forming **32**, which then recycles to give the 1*H*-pyrrolo[2,1-*c*][1,4]-thiazine (**34**). The 1:2-molar adduct **33** was obtained from the appropriate bromo derivative of **30**; in this case the hydroxyl group of the presumed pyrrolothiazine formed (cf. **34**) combined with another mole of EP.

Thiazole-*N*-imines (**36**) are reported⁵⁵³ to give (**37**) with DMAD, but the possibility of rearrangement was not considered. In the case of the imide derived from **38** the product is stated to be **39**,⁵⁵³ and here rearrangement is less likely to have taken place.



Boekelheide and Fedoruk⁵⁵⁴ prepared the thiazolium ylid **40** and obtained the adduct formulated as **41**.



E. MESOIONIC THIAZOLES

Potts and Roy⁵⁵⁵ showed that cycloaddition of DMAD occurs with ease to the mesoionic thiazolones **42** and **43**. After 15 hours reflux in

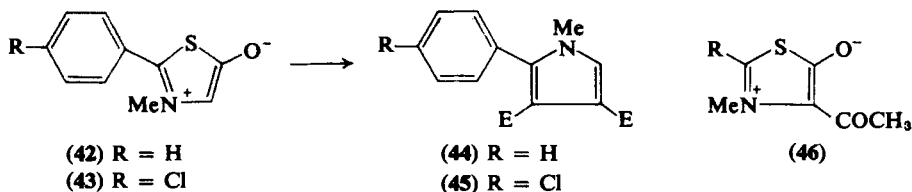
⁵⁵² K. T. Potts, D. R. Choudhury, and T. R. Westbry, *J. Org. Chem.* **41**, 187 (1976).

⁵⁵³ H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 482 (1974).

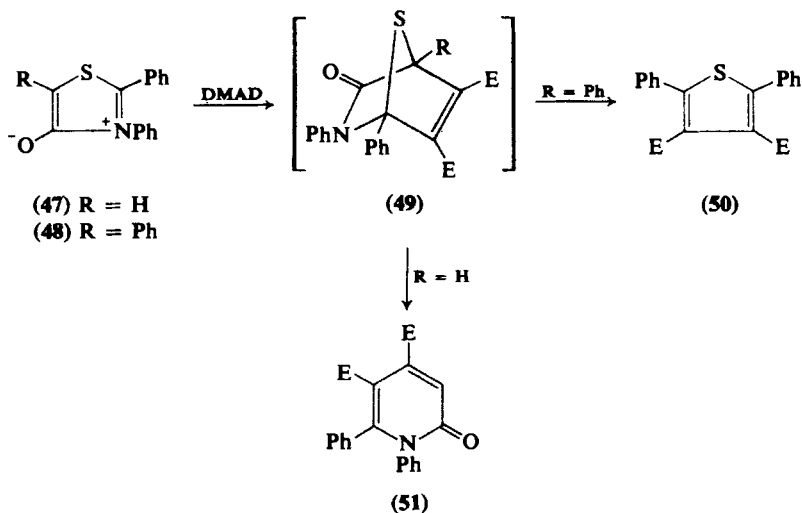
⁵⁵⁴ V. Boekelheide and N. Fedoruk, *J. Am. Chem. Soc.* **90**, 3830 (1968).

⁵⁵⁵ K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061 (1968).

benzene, 66% of the pyrroles **44** and **45** were obtained. This was the first example of the elimination of carbonyl sulfide from a cycloaddition reaction. The cycloaddition did not occur when the acylated derivative **46** was used.^{556,557} Potts and co-workers⁵⁵⁸ have described the interesting cycloadditions of DMAD to the isomeric anhydro-4-hydroxythiaz-



olium hydroxides **47** and **48**. The initial cycloadduct **49**, which was not isolated, decomposed with extrusion of sulfur to the pyridone **51** (90%) in the case of **47**, whereas under the same conditions **48** gave 70% of the thiophene-3,4-dicarboxylate **50** with elimination of phenyl isocyanate.



F. THIAZOLINES, THIAZOLINONES, AND THIAZOLINIMINES

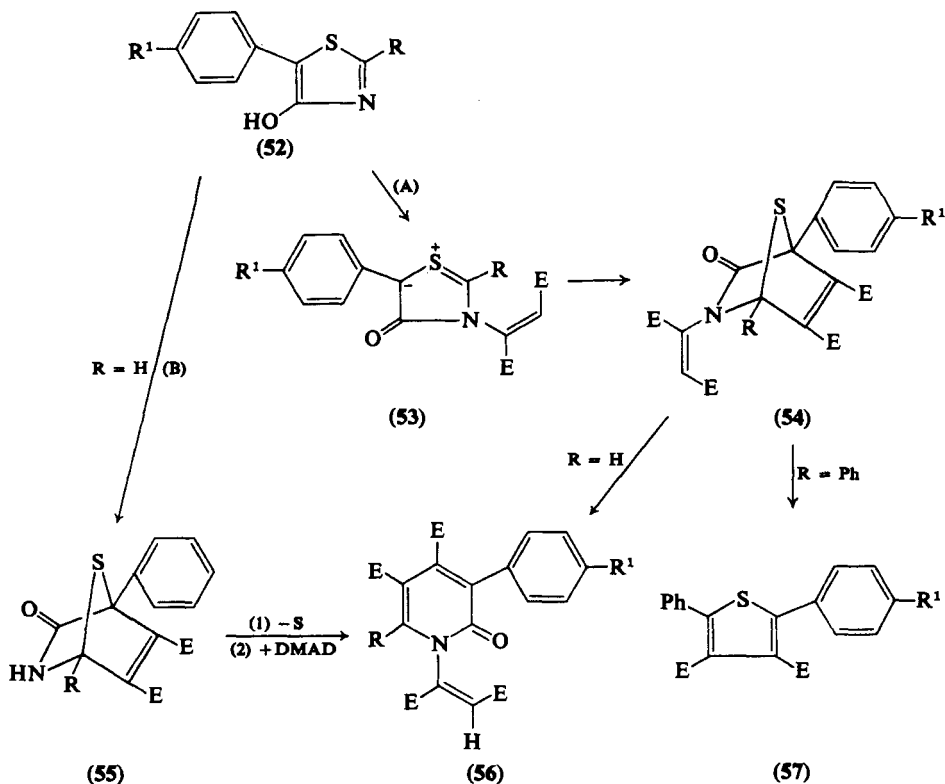
4-Hydroxythiazoles (thiazolin-4-ones) (**52**) are potential thiocarbonyl ylids (cf. **113**) and ought to undergo 1,3-dipolar cycloadditions by

⁵⁵⁶ A. Lawson and C. E. Searle, *J. Chem. Soc.*, 1556 (1957).

⁵⁵⁷ M. Ohta and C. Shin, *Bull. Chem. Soc. Jpn.* **38**, 704 (1965).

⁵⁵⁸ K. T. Potts, E. Houghton, and U. P. Singh, *Chem. Commun.*, 1129 (1969); *J. Org. Chem.* **39**, 3627 (1974).

analogy with Δ^2 -oxazolin-4-ones, which behave as carbonyl ylids.^{559,560} Michael-type addition of DMAD to **52** gives the ylid **53**, which adds a second mole of ester to produce **54** which in turn fragments to the pyridone **56** and the thiophene **57** corresponding to **51** and **50**. An alternative path, involving fragmentation of adduct **55** and Michael addition of the second mole of acetylene at the pyridone stage, was considered unlikely.



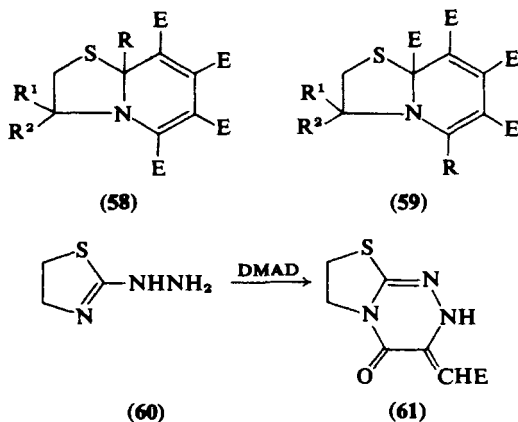
The addition of 2-methyl-, 2-ethyl-, 4-ethyl-, and 4,4-dimethyl- Δ^2 -thiazolines to DMAD in DMF for several days gave 1:2-molar adducts. These have been formulated⁵⁶¹ as **58**, but their ¹H nmr spectra show⁵⁴³ that they have isomerized to **59**, as in the case of most of the adducts of thiazole (see the foregoing). 2-Hydrazino- Δ^2 -thiazoline (**60**) with DMAD gave adduct (**61**).⁵⁶²

⁵⁵⁹ K. T. Potts and J. Marshall, *Chem. Commun.*, 1000 (1972).

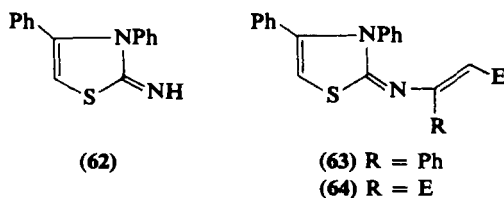
⁵⁶⁰ A. Robert, M. Ferrey, and A. Foucaud, *Tetrahedron Lett.*, 1377 (1975).

⁵⁶¹ J. Roggero and C. Divorne, *C. R. Acad. Sci., Ser. C* **268**, 870 (1969).

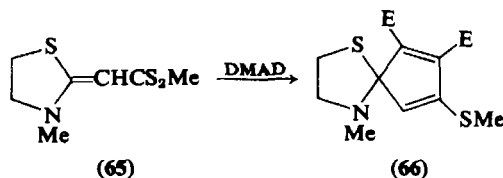
⁵⁶² D. J. LeCount and A. T. Greer, *Tetrahedron Lett.*, 2905 (1973).



2-Imino-3,4-diphenylthiazoline (62) with EPP and with DMAD gave Michael adducts 63 and 64, respectively.⁵⁶³



Reaction of the thiazoline ester (65) with DMAD gave the spiroadduct 66, with extrusion of sulfur.⁵⁶⁴

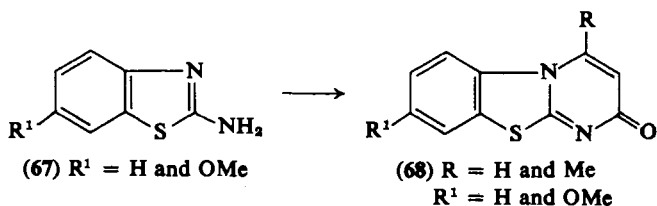


G. FUNCTIONALLY SUBSTITUTED BENZOTHAZOLES

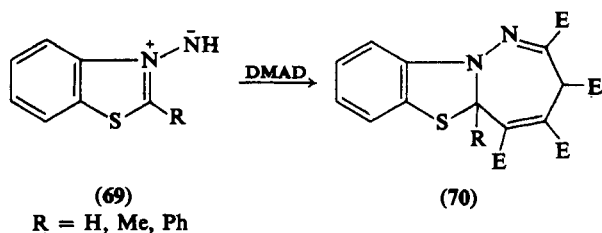
Addition of propiolic and tetrolic esters to the 2-aminobenzothiazoles 64 gave adducts 68.^{484,550} Some of these compounds are said to be

⁵⁶³ K. Akiba, M. Ochiumi, T. Tsuchiya, and N. Inamoto, *Tetrahedron Lett.*, 459 (1975).

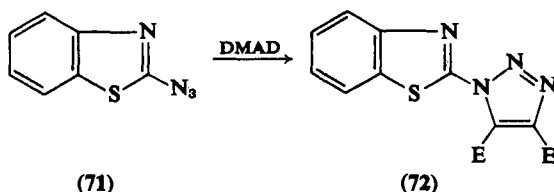
⁵⁶⁴ G. Kobayashi, Y. Matsuda, Y. Tominaga, and K. Mizuyama, *Heterocycles* 2, 309 (1974) [*CA* 81, 49,611 (1974)].



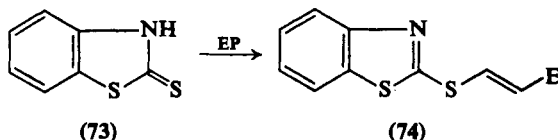
amebicidal and antifungal. *N*-Imino derivatives of benzothiazoles (69) gave the 2:1 adducts 70 with DMAD (however, compare 37).⁵⁵³



Addition product 72 from 2-azidobenzothiazole (71) was claimed to have anthelmintic and nematocidal activity.⁴⁸³ Refluxing EP with



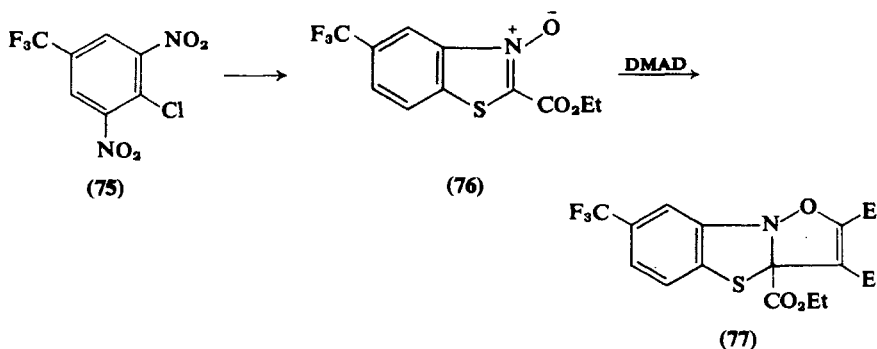
2-benzothiazolethione (73) in absolute ethanol gave the Michael-type adduct 74.⁵⁶⁵ The *o*-nitrochlorobenzene (75) and thioglycollic ester



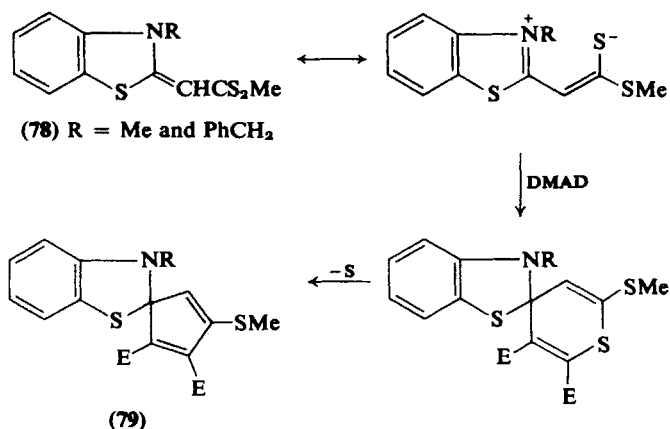
gave benzthiazole *N*-oxide (76), which combined with DMAD in chloroform to give 59% of the adduct 77.⁵⁶⁶

⁵⁵⁵ E. I. Grinblat and I. Y. Postovskii, *Dokl. Akad. Nauk SSSR* 133, 847 (1960). [*CA* 54 24756 (1960)]; *Zh. Obshch. Khim.* 31, 394 (1961) [*CA* 55, 22,298 (1961)].

⁵⁶⁶ K. Wagner, H. Heitzer, and L. Oehlmann, *Chem. Ber.* 106, 640 (1973).



Kobayashi *et al.*⁵⁶⁴ reacted benzothiazole α -dithiocarboxylates (78) with DMAD in DMF to give the adducts 79. Similar desulfurizations following an initial addition have been described.^{567,568}



Spiro[benzothiazolinepyridines] (81) were obtained in moderate yields by treatment of 1-aryl-3-[3-methylbenzothiazol-2-ylidene]triazene (80) with DMAD in dry DMF for 5 hours at 90°–100°. Hydrolysis of 81 ($\text{R} = \text{Cl}$) gave 80% of the pyridone 82.⁵⁶⁹

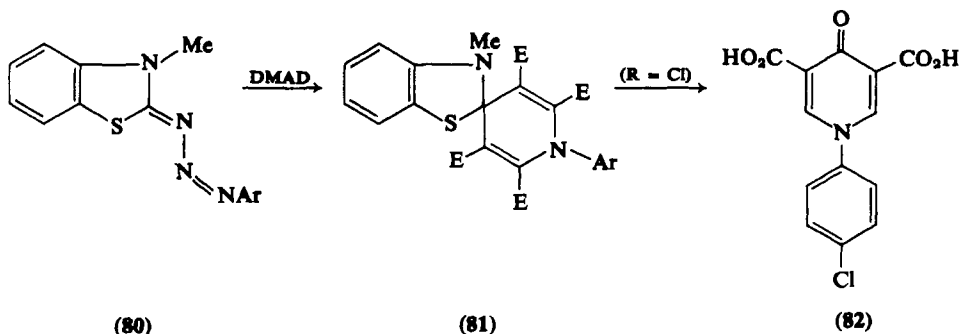
Ethyl 2-benzothiazolylpyruvate with hot DMAD alone gives a mixture of 83, 84, and 85,⁵⁷⁰ which can be formed by initial nucleophilic attack from the highly activated methylene group.

⁵⁶⁷ D. M. McKinnon and J. M. Buchsriber, *Can. J. Chem.* **49**, 3299 (1971).

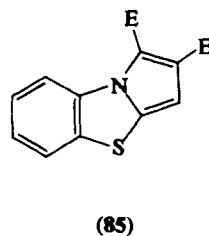
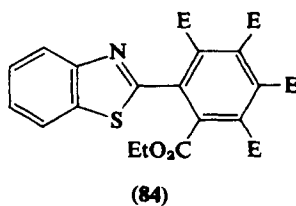
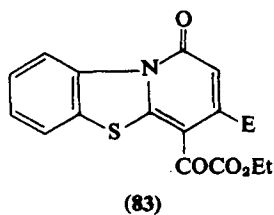
⁵⁶⁸ D. N. Reinhoudt and C. G. Kouwenhoven, *Chem. Commun.*, 1232 (1972).

⁵⁶⁹ E. Fanghoenel, R. Ebisch, and P. Niedermayer, *Z. Chem.* **15**, 143 (1975) [*CA* **83**, 97,110 (1975)].

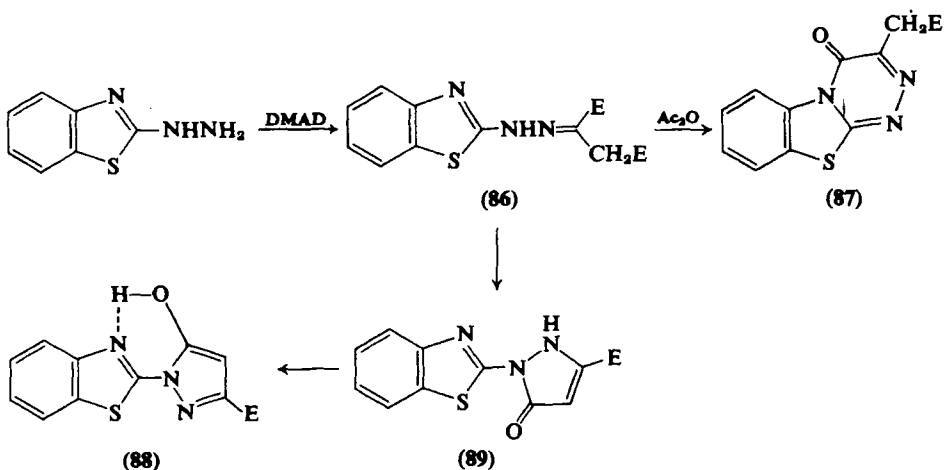
⁵⁷⁰ R. M. Acheson and W. R. Tully, *J. Chem. Soc. C*, 1623 (1968).



(80)
 $\text{Ar} = p\text{-C}_6\text{H}_4\text{R}$;
 $\text{R} = \text{Cl}, \text{NO}_2, \text{OMe}, \text{Me}$



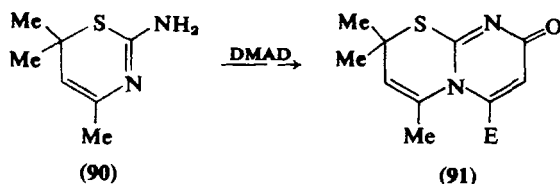
Treatment of 2-hydrazinobenzothiazole with DMAD gave the primary adduct 86, which, on warming, gave the pyrazole 89.⁵⁷¹ Heating the latter to 100° *in vacuo* gave 88. Ring closure of 86 with acetic anhydride gave 87.



⁵⁷¹ D. J. LeCount and A. T. Greer, *J. Chem. Soc., Perkin Trans. 1*, 297 (1974).

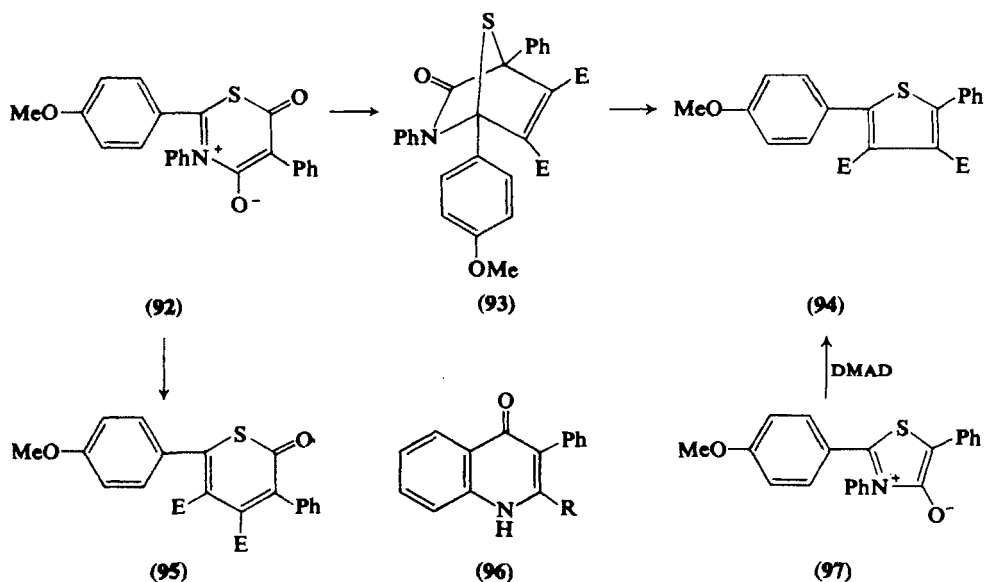
H. 1,3-THIAZINES

Addition of DMAD at 0° in ether to 2-amino-4,6,6-trimethyl-1,3-thiazine (90) gave 72% of the adduct 91.⁵⁷²



I. MESOIONIC 1,3-THIAZINES

Potts, Ehrlinger, and Nichols⁵⁷³ treated the mesoionic 1,3-thiazine betaine (92) with DMAD and obtained the thiophene 94 (28% yield), which was also synthesized from 97 and DMAD. Some 96 (R = 4-MeOC₆H₄) was also formed through rearrangement of the starting material. Product 94 could arise from 93 by loss of phenyl isocyanate or from 95 by loss of carbon monoxide. Replacement of the *p*-methoxy-



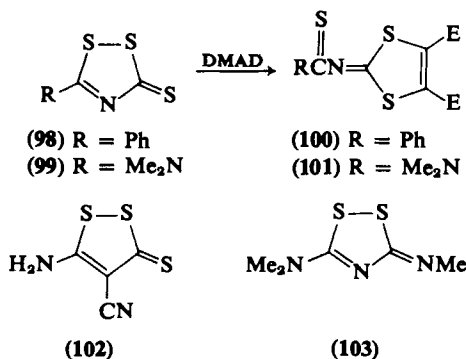
⁵⁷² M. N. Sharma, *Curr. Sci.* 43, 147 (1974).

⁵⁷³ K. T. Potts, R. Ehrlinger, and W. M. Nichols, *J. Org. Chem.* 40, 2596 (1975).

phenyl moiety in **92** by *N*-methylphenylamino completely suppressed the cycloaddition and only **96** ($R = \text{PhMeN}$) was obtained.

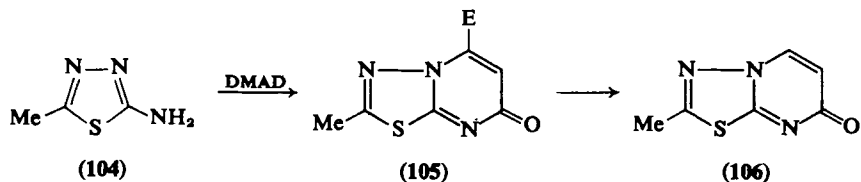
J. 1,2-DITHIOLES AND 1,2,4-DITHIAZOLES

Dimethyl acetylenedicarboxylate adds to **98**⁵⁷⁴ and **99**⁵⁷⁵ to give the 1:1-molar adducts **100** and **101**, the original ring being opened, and similar reactions have been observed with **102**⁵⁷⁶ and **103**.⁵⁷⁵



K. 1,3,4-THIADIAZOLES

2-Amino-5-methyl-1,3,4-thiadiazole **104** gave the adduct **105** with DMAD; hydrolysis and decarboxylation of the latter gave **106**.⁵⁷⁷



Mesoionic 1,3,4-thiadiazoles of type **107** and **108** were originally reported not to give cycloadducts with DMAD but surprisingly added to diethyl azodicarboxylate.⁵⁷⁸⁻⁵⁸⁰ Later, Moriarty and Chin⁵⁸¹ reported

⁵⁷⁴ H. Behringer, D. Bender, J. Falkenberg, and R. Wiedenmann, *Chem. Ber.* **101**, 1428 (1968).

⁵⁷⁵ J. E. Oliver and R. T. Brown, *J. Org. Chem.* **39**, 2228 (1974).

⁵⁷⁶ K. Gewald, *J. Prakt. Chem.* **31**, 214 (1966).

⁵⁷⁷ A. Shafi'ee and I. Lalezari, *J. Heterocycl. Chem.* **12**, 675 (1975).

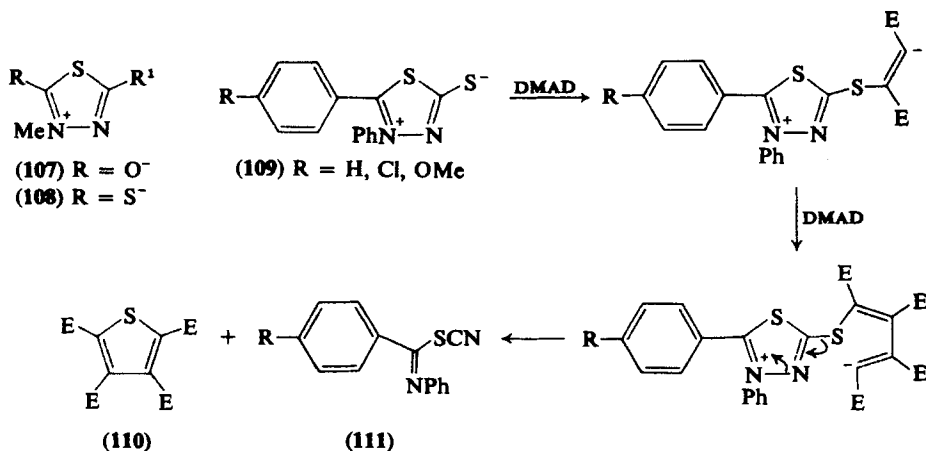
⁵⁷⁸ K. T. Potts and C. Sapino, *Chem. Commun.*, 672 (1968).

⁵⁷⁹ R. M. Moriarty, J. M. Kliegman, and R. B. Desai, *Chem. Commun.*, 1045 (1967).

⁵⁸⁰ W. L. Mosby, *Chem. Commun.*, 837 (1971).

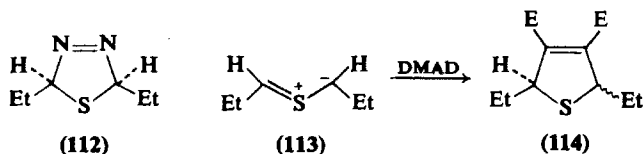
⁵⁸¹ R. M. Moriarty and A. Chin, *Chem. Commun.*, 1300 (1972).

that refluxing DMAD with **109** in benzene for 6 hours gave 30% of tetramethyl thiophenetetracarboxylate (**110**) and about 50% of *S*-cyanothioimidates (**111**); the mechanism shown was postulated.



L. 1,3,4-THIADIAZOLINES

Δ^3 -Thiadiazolines (**112**) are unstable, losing nitrogen to yield thio-carbonyl ylids (**113**), which have been trapped with DMAD and other dienophiles.⁵⁸² Hence, by allowing **112** to warm to room temperature in the presence of DMAD, 20% of **114** was obtained. Although



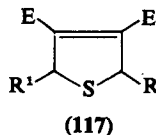
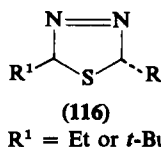
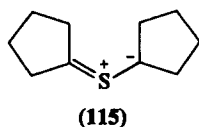
attempts to trap the more highly substituted ylid **115** with DMAD failed, success was obtained with azodicarboxylic ester. Thermolysis of **116** in the presence of DMAD gave **117**. Many reactions of this type have been carried out.⁵⁸³⁻⁵⁸⁵

⁵⁸² R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970).

⁵⁸³ J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.* 37, 4045 (1972).

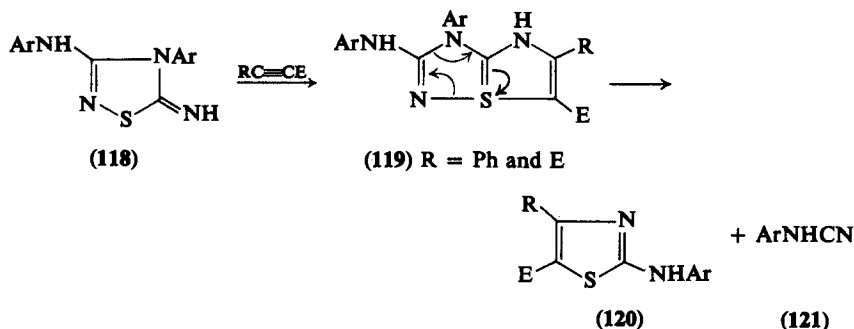
⁵⁸⁴ W. L. Prins and R. M. Kellogg, *Tetrahedron Lett.*, 2833 (1973).

⁵⁸⁵ R. M. Kellogg and W. L. Prins, *J. Org. Chem.* 39, 2366 (1974).



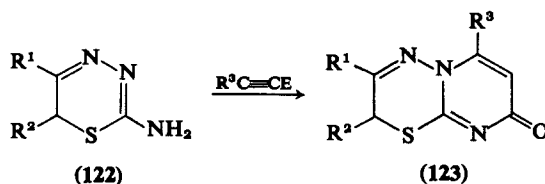
M. 1,2,4-THIADIAZOLIDINES

Additions of MPP and DMAD to "Hector's bases" (118) are considered to proceed via 6a-thia(S^{IV})-1,3,4-triazapentalenes (119), which decompose to give thiazoles (120) and the *N*-cyanoaniline 121.⁵⁸⁸



N. 1,3,4-THIADIAZINES

Pyrimidothiadiazines (123) have been prepared from acetylenic esters and the aminothiadiazines 122,⁵⁸⁷



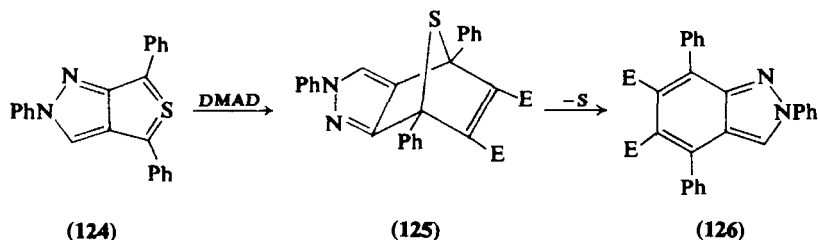
O. THIENOPYRAZOLES

Refluxing the thieno[3,4-*c*]pyrazole 124 with DMAD in benzene gave 76% of the adduct 125, which readily lost sulfur giving 126.⁵⁸⁸ A

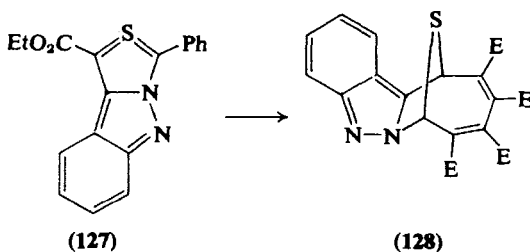
⁵⁸⁸ K. Akiba, M. Ochiuni, T. Tsuchiya, and N. Inamoto, *Tetrahedron Lett.*, 459 (1975).

⁵⁸⁷ Sankyo Co., Japanese Patent 74,110,696 [*CA* 82, 171,096 (1975)].

⁵⁸⁸ K. T. Potts and D. McKeough, *J. Am. Chem. Soc.* 96, 4276 (1974).



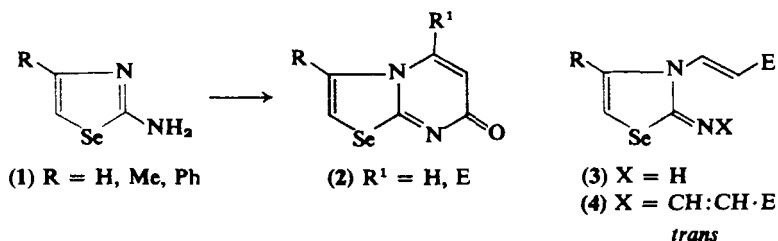
1:2-molar adduct **128** has been obtained from **127** with DMAD.⁵⁸⁹



XI. Compounds from Heterocycles Containing Nitrogen and Selenium

A. SELENAZOLES

2-Aminoselenazoles (**1**) with DMAD gave 7*H*-selenazolo[3,2-*a*]pyridinidin-7-ones (**2**, $R' = E$), whereas EP yielded **2** ($R' = H$) and the Michael-type adducts **3** and **4**.⁵⁹⁰

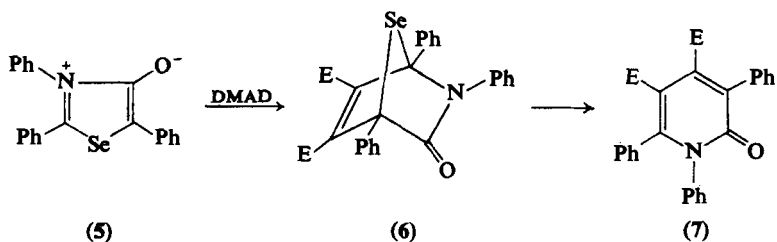


⁵⁸⁹ K. T. Potts and J. L. Marshall, *J. Org. Chem.* **41**, 129 (1976).

⁵⁹⁰ K. T. Potts, E. Houghton, and U. P. Singh, *J. Org. Chem.* **39**, 3627 (1974).

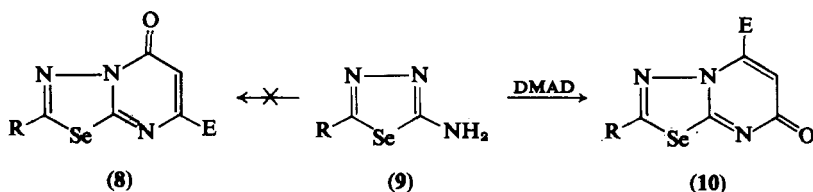
B. MESOIONIC SELENAZOLES

Cava and Saris⁵⁹¹ refluxed the mesoionic selenazole **5** for a week with DMAD in benzene, and obtained 65% of the pyridone **6**. This may be compared with the analogous mesoionic thiazole **49** (Section X,E). The easy loss of selenium from **6** contrasts with the loss of phenyl isocyanate from **49**.



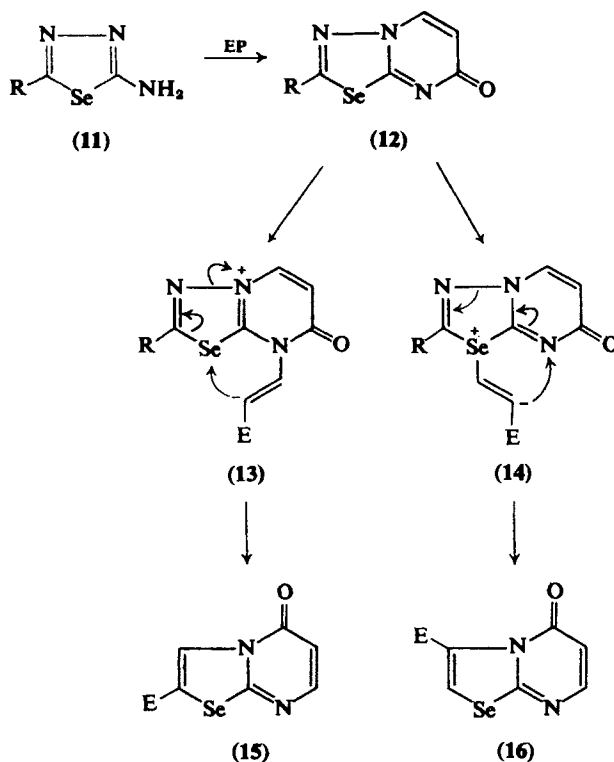
C. 1,3,4-SELENADIAZOLES

2-Amino-1,3,4-selenadiazoles (**9**) with DMAD give 7*H*-1,3,4-selenadiazolo[3,2-*a*]pyrimidin-7-ones (**10**) and not the isomeric 5-ones **8**. With EP different reactions via **13** or **14** yield the 5*H*-selenazolo[3,2-*a*]-



pyrimidin-5-ones **15** or **16**. Structural assignments were based on the spectra of the compounds and on comparison with the corresponding sulfur analogs.⁵⁷⁷

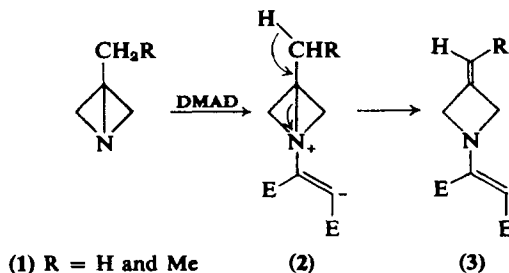
⁵⁹¹ M. P. Cava and L. E. Saris, *Chem. Commun.*, 617 (1975).



XII. Compounds from Heterocycles Containing Nitrogen at a Bridgehead Position

A. 1-AZABICYCLO[1,1,0]BUTANES

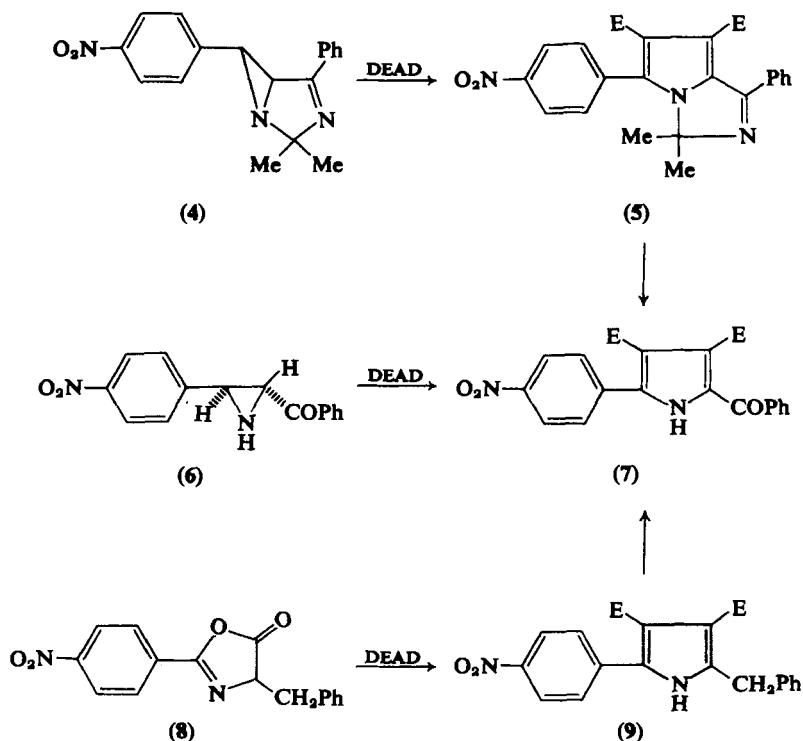
1-Azabicyclo[1,1,0]butane (1) with DMAD gave the azetidine 3 presumably via the intermediate 2.⁵⁹²



⁵⁹² W. Funke, *Chem. Ber.* **102**, 3148 (1969).

B. 1,3-DIAZABICYCLO[3,1,0]HEXENES

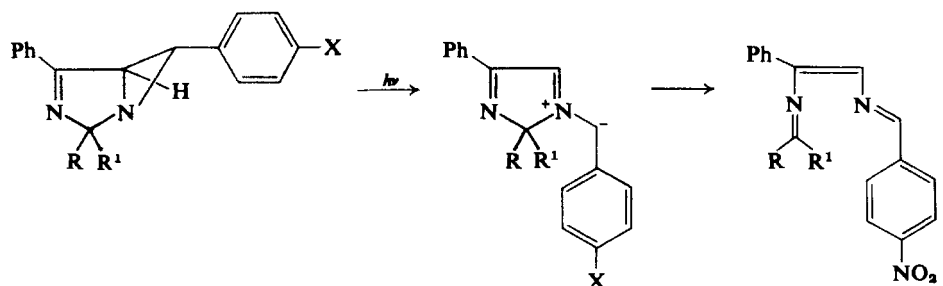
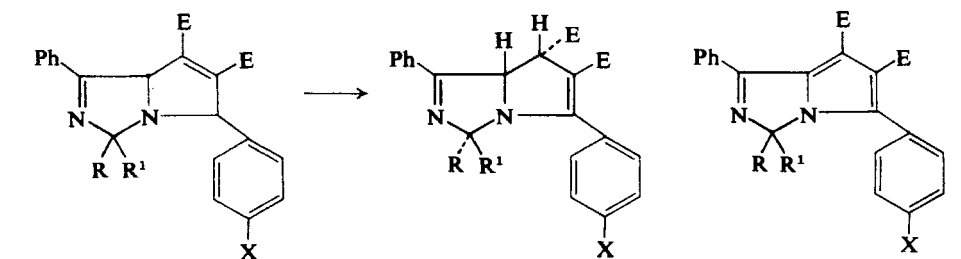
Heine and co-workers⁵⁹³ prepared the adduct **5** from 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3,1,0]hex-3-ene (**4**) and DEAD in refluxing xylene; acid hydrolysis gave (**7**). The aroylaziridine **6** with DEAD also gave **7** (14%), as did the oxazolin-5-one **8** and DEAD via the benzylpyrrole **9**.



DoMinh and Trozzolo⁵⁹⁴ discovered that the red color obtained by photolysis of **10** was discharged by the addition of DMAD; in the absence of trapping agent, compound **12** was obtained. Continued irradiation in the presence of the dipolarophile led to **14**, different from the expected primary adduct **13**. Refluxing with palladium on charcoal in benzene, converted **14** into **15**. When **10** and DMAD were heated together in toluene, 40% of **14** and 30% of **15** were obtained.⁵⁹³

⁵⁹³ H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.* **33**, 1097 (1968).

⁵⁹⁴ T. DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.* **92**, 6998 (1970).

(10) $R = R^1 = \text{Me}$, $X = \text{NO}_2$ (16) $R = X = \text{H}$, $R^1 = \text{Ph}$ (11) $R = R^1 = \text{Me}$, $X = \text{NO}_2$ (17) $R = X = \text{H}$, $R^1 = \text{Ph}$ (12) $R = R^1 = \text{Me}$ (13) $R = R^1 = \text{Me}$, $X = \text{NO}_2$ (14) $R = R^1 = \text{Me}$, $X = \text{NO}_2$ (18) $R = X = \text{H}$, $R^1 = \text{Ph}$ (15) $R = R^1 = \text{Me}$, $X = \text{NO}_2$ (19) $R = X = \text{H}$, $R^1 = \text{Ph}$

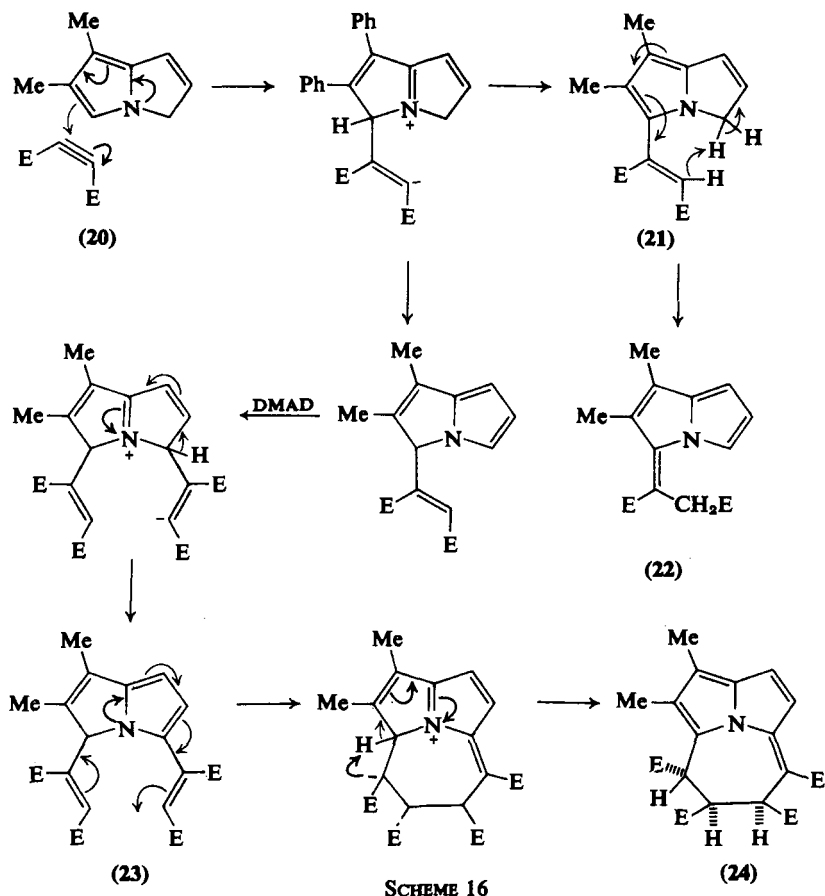
Padwa and Glazer⁵⁹⁵ described similar 1,3-dipolar cycloaddition reactions of the azomethine ylid **17** (cf. **11**). Irradiation of **16** in an ethanol glass at liquid nitrogen temperature produced the bright red ylid **17**; repetition at 77 K in the presence of DMAD gave a red coloration rapidly discharged on warming to produce a single cycloadduct **18** whose stereochemistry was deduced from its NMR spectrum. Palladium on charcoal readily dehydrogenated **18** to **19**.

C. PYRROLIZINES

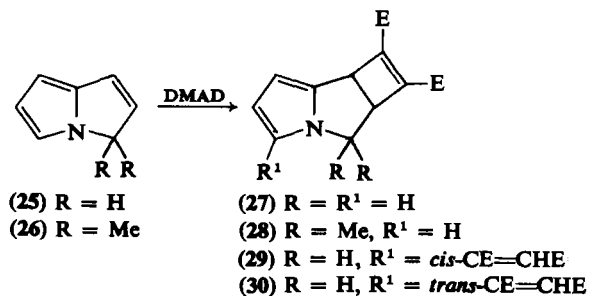
Johnson and Jones,⁵⁹⁶ obtained a 1:1-molar adduct **22** from DMAD and DEAD and a number of 3*H*-pyrrolizines (e.g., **20**) by the route (Scheme 16) shown. The proposed mechanism via **21**, was in accordance with the results of deuterium labeling experiments. Reaction between **20** and excess of DMAD gave the 1:2 adduct **24** via the intermediate dimaleate **23**, which could be isolated.

⁵⁹⁵ A. Padwa and E. Glazer, *J. Am. Chem. Soc.* **94**, 7788 (1972); *J. Org. Chem.* **38**, 284 (1973).

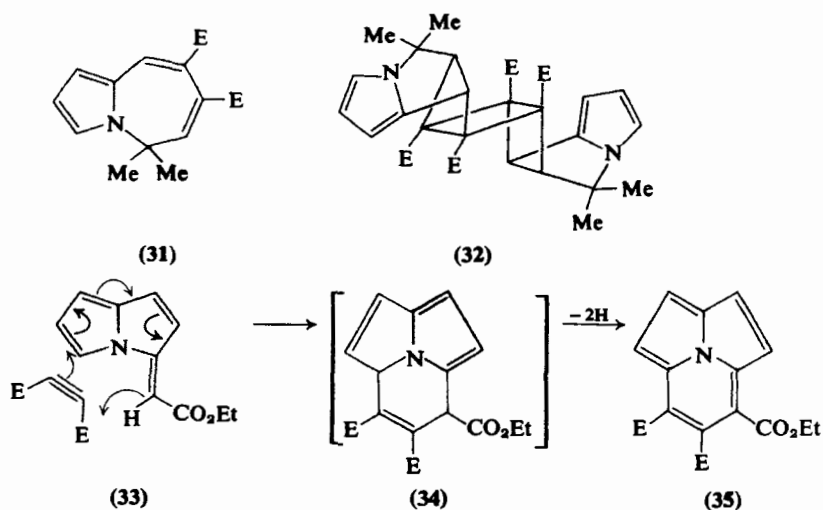
⁵⁹⁶ D. Johnson and G. Jones, *J. Chem. Soc., Perkin. Trans. 1*, 840, 844, 2517 (1972).



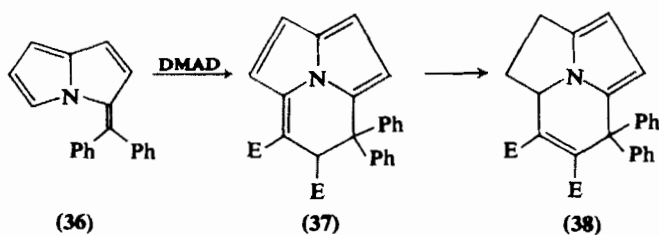
The photochemical addition⁵⁹⁸ of DMAD to 3*H*-pyrrolizine (**25**) and to 3,3-dimethyl-3*H*-pyrrolizine (**26**) gave low yields of adducts **27** and **28**; from **25** the 8-maleate and fumarate derivatives (**29** and **30**) were also obtained. Thermolysis of **28** gave **31**, whereas photolysis gave the



dimer **32**; reaction of 3-ethoxycarbonylmethylene-3*H*-pyrrolizine (**33**) with DMAD gave the pyrrolo[2,1,5-*cd*]indolizine triester (**35**), the intermediate (**34**) rapidly becoming oxidized in order to provide the aromatic delocalization energy associated with the peripheral π -electron system of the cyclazine.

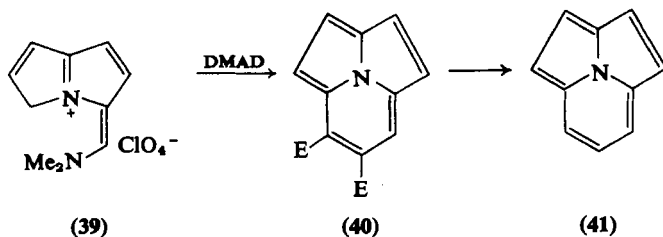


Diphenylmethylene-3*H*-pyrrolizine (**36**) underwent cycloaddition with DMAD to give **37**, which could be reduced to **38**.⁵⁹⁶



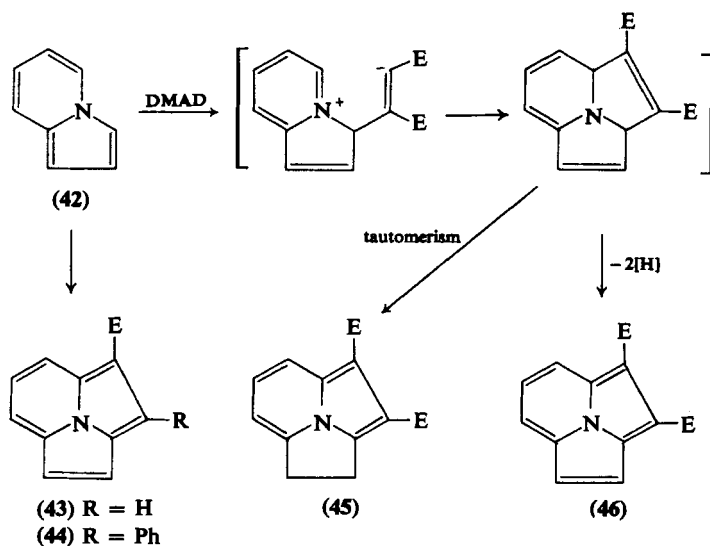
Jesse and Leaver⁵⁹⁷ reacted 3*H*-pyrrolizine (**25**) with the Vilsmeier reagent in THF and isolated the product, presumably **39**, as the perchlorate. Treatment of the latter with DMAD and sodium hydride gave dimethyl cycl[3,2,2]azine-5,6-dicarboxylate (**40**), which was hydrolyzed and decarboxylated to the parent ring system (**41**).

⁵⁹⁷ M. A. Jesse and D. Leaver, *Chem. Commun.*, 790 (1970).



D. INDOLIZINES

Indolizine (42) combined with DMAD in the presence of palladium on charcoal yielding two products (45, 46), which may be formed as indicated (Scheme 17).⁵⁹⁸

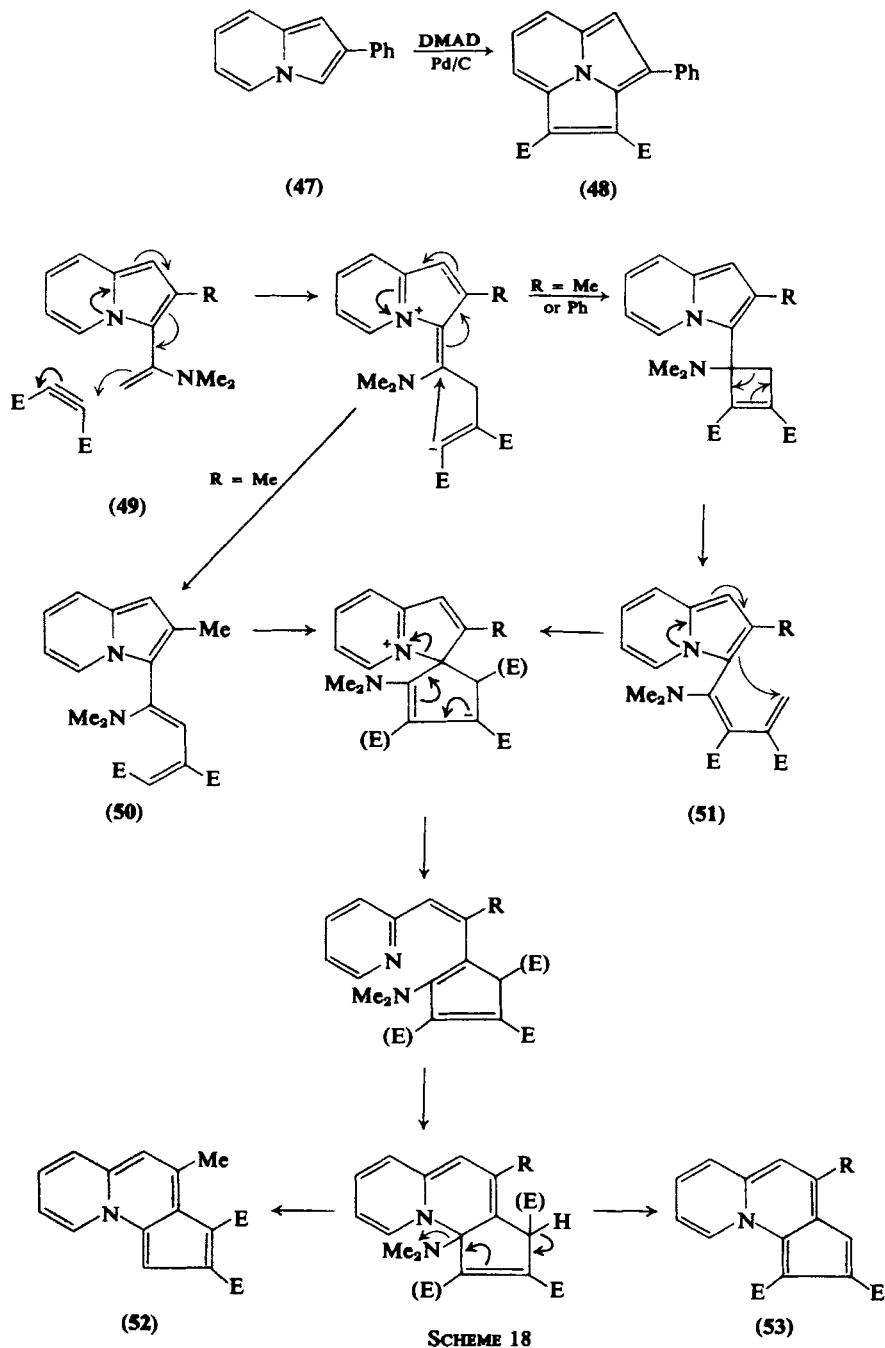


SCHEME 17

Methyl propiolate and EPP add to indolizine giving 43 and 44; the structure of the latter was confirmed by hydrolysis and decarboxylation to a known compound.⁵⁹⁷ Substituted indolizines react as well; Boekelheide and Fahrenholtz converted 2-phenylindolizine (47) into 48 under these same conditions.⁵⁹⁹

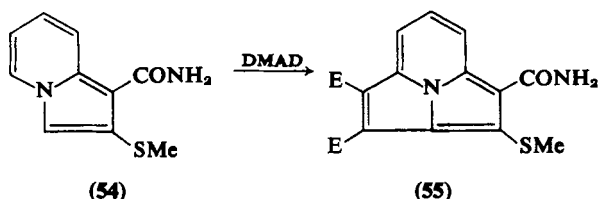
⁵⁹⁸ A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.* **24**, 582 (1959); A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.* **83**, 453 (1961).

⁵⁹⁹ V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.* **83**, 458 (1961).



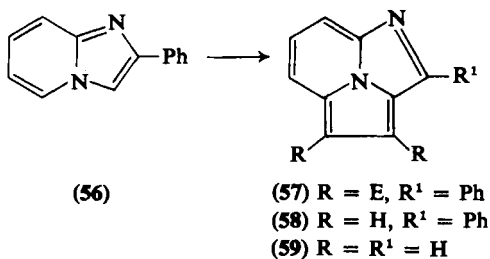
Thermal addition of DMAD to 3-(1'-dimethylaminovinyl)indolizine (49; R = Me or Ph) in toluene gave cyclopenta[*c*]quinolizine (53) via a cyclobutene⁶⁰¹ and the diene 51 (Scheme 18). Formation of 53 involves a rearrangement apparently without precedent. By carrying out the addition in methanol, the zwitterion was intercepted by proton transfer to give 50, which was converted into the isomeric quinolizine 52 in boiling xylene.⁶⁰⁰

Addition of DMAD to the indolizine (54) gave 55.⁶⁰²



E. IMIDAZO[1,2-*a*]PYRIDINES

Boekelheide and Miller⁶⁰³ heated 2-phenyl-1-azaindolizine (56) with DMAD and palladium:charcoal and isolated 57 in 29% yield; hydrolysis and decarboxylation gave the parent ring system (58), but attempts to make 59 were thwarted by their inability to make the unsubstituted 1-azaindolizine. Boekelheide and Kertelj⁶⁰⁴ heated 60



with DMAD and palladium:charcoal in toluene and obtained 28% of adduct 61, which, on hydrolysis and decarboxylation, gave 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (62).

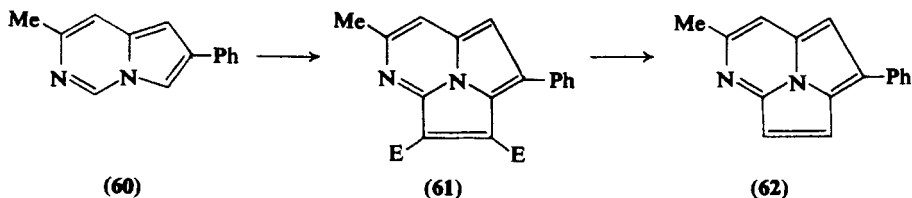
⁶⁰⁰ W. K. Gibson and D. Leaver, *Proc. Chem. Soc.*, 330 (1964); *J. Chem. Soc. C*, 324 (1966).

⁶⁰¹ G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.* **28**, 1459 (1963).

⁶⁰² C. Maseda and G. Kobayashi, *J. Pharm. Soc.* **94**, 839 (1974).

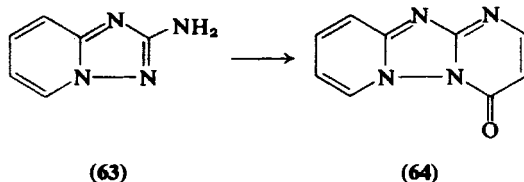
⁶⁰³ V. Boekelheide and A. Miller, *J. Org. Chem.* **26**, 431 (1961).

⁶⁰⁴ V. Boekelheide and S. S. Kertelj, *J. Org. Chem.* **28**, 3212 (1963).



F. TRIAZOLO[1,5-*a*]PYRIDINES

2-Aminotriazolo[1,5-*a*]pyridine (63) on treatment with propiolic ester gave **64**.⁶⁰⁵



G. CYCL[3,3,3]AZINES (9*b*-AZAPHENALENES)

Treatment of the cycl[3,3,3]azine (9*b*-azaphenalene) (**66**) with DMAD in benzene at 20° gave adducts **65** and **68**. When **68** was heated with DMAD in benzene the 1:2-molar adduct **69** was obtained.^{600,606} A similar adduct of EPP to **67** was described.

H. PYRIDO[1,2-*b*]CINNOLINES

Anhydro-11-hydroxypyrido[1,2-*b*]cinnolin-6-ium hydroxide (**70**) with DMAD gave the pyridylquinolone (**71**), established by X-ray crystallography.⁶⁰⁷

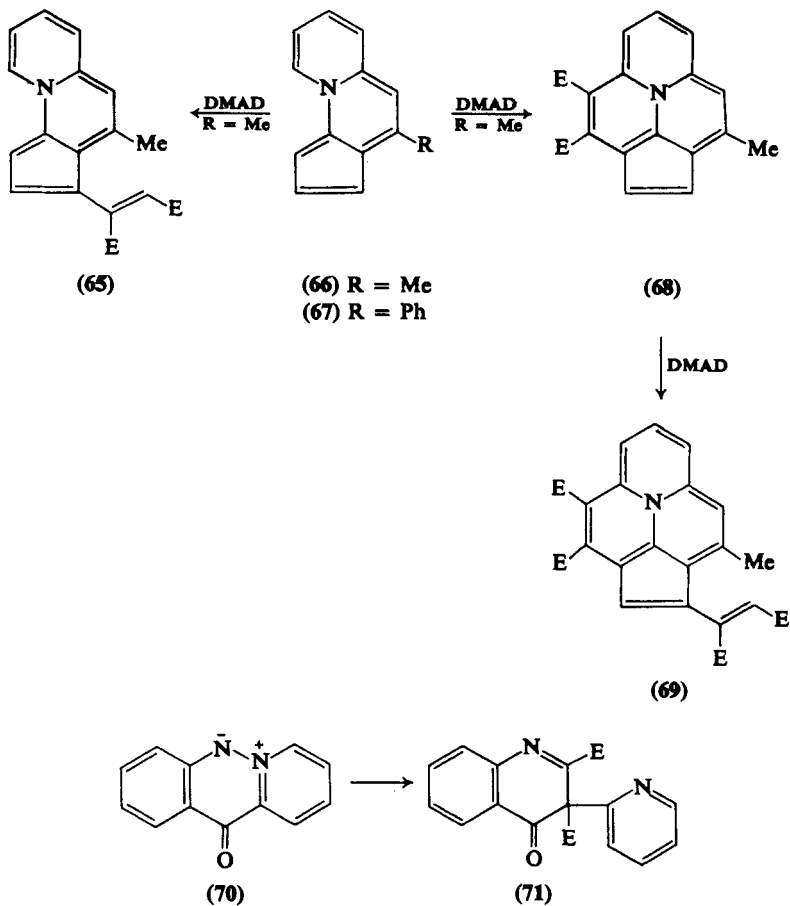
I. PYRIDO[1,2-*c*]PYRIDINES

1-Cyano-4-imino-2-methylthio-4*H*-pyrido[1,2-*c*]pyridine (**72**), obtained from 2-pyridylacetonitrile, and dimethyl cyanamidedithiocar-

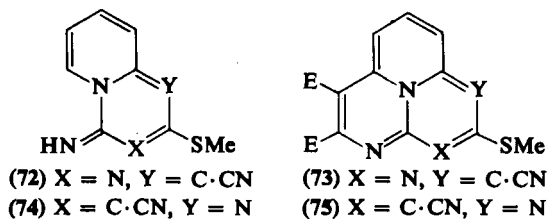
⁶⁰⁵ H. Reimlinger, M. A. Peiven, and R. Merényi, *Chem. Ber.* **105**, 794 (1972).

⁶⁰⁶ W. K. Gibson and D. Leaver, *Chem. Commun.*, 11 (1965); R. P. Cunningham, D. Farquhar, W. K. Gibson, and D. Leaver, *J. Chem. Soc. C*, 239 (1969).

⁶⁰⁷ R. Y. Ning, J. F. Blount, W. Y. Chen, and P. B. Madan, *J. Org. Chem.* **40**, 2201 (1975).



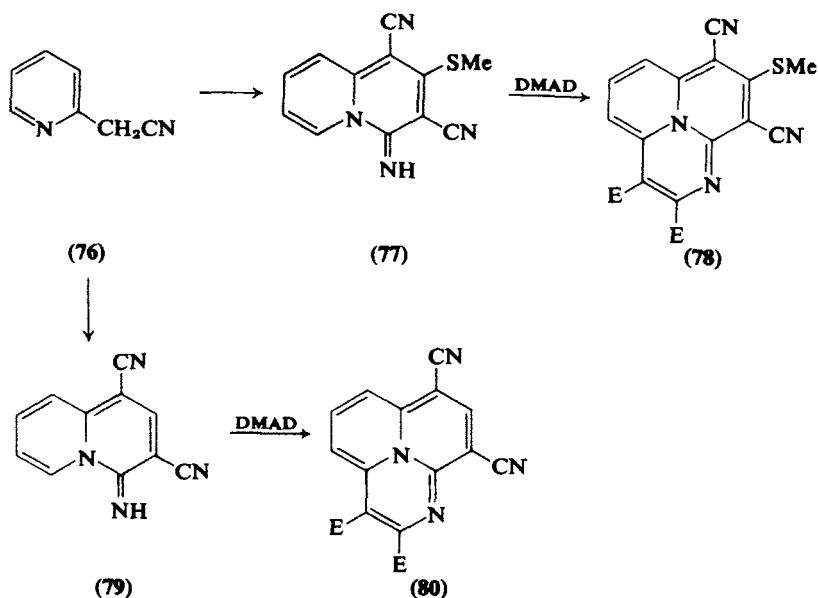
boxylate gave the 1,9-diazacycl[3,3,3]azine (73) with DMAD; by a similar process 74 gave the isomeric adduct 75.⁶⁰⁸



⁶⁰⁸ H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *J. Pharm. Soc.* **95**, 13 (1975).

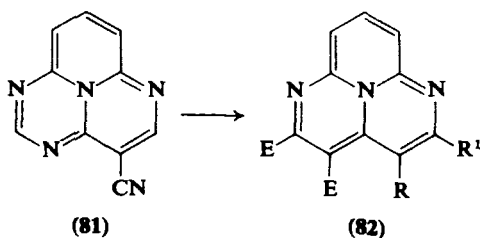
J. QUINOLIZINES

1,3-Dicyano-4-imino-2-methylthio-4*H*-quinolizine (77), obtained from (76) and 2-cyano-3,3-bis(methylthio)acrylonitrile, gave the adduct 78 with DMAD in DMF. Pyridine 76 formed 79 with ethoxymethylene-malononitrile, and subsequent treatment with DMAD in DMF yielded 80.⁶⁰⁹



K. 1,3,6-TRIAZACYL[3,3,3]AZINES

Kobayashi *et al.*⁶¹⁰ found that the course of the addition of DMAD to 4-cyano-1,3,6-triazacyl[3,3,3]azine (81) is dependent on the solvent



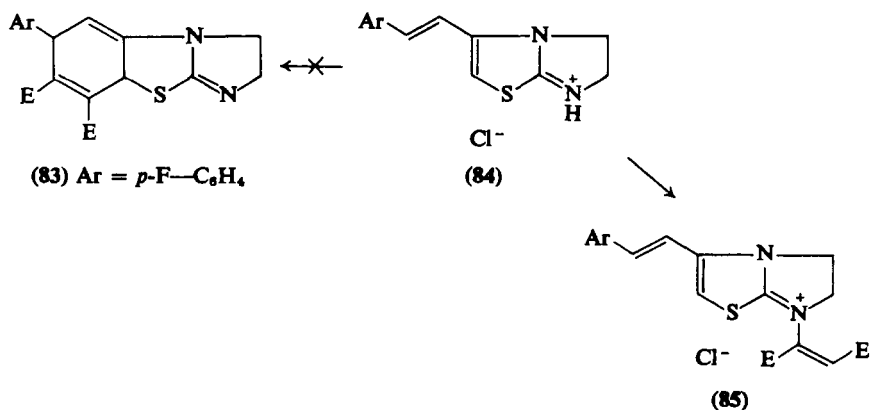
⁶⁰⁹ G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, C. Maseda, and H. Awaya, *J. Pharm. Soc.* **94**; 50 (1974).

⁶¹⁰ K. Kurata, M. Matsuo, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **23**, 1629 (1975).

employed. In DMF the product was **82** ($R = \text{CN}$, $R' = \text{H}$), whereas in acetonitrile product **82** with $R = R' = \text{E}$ was obtained.⁶¹⁰

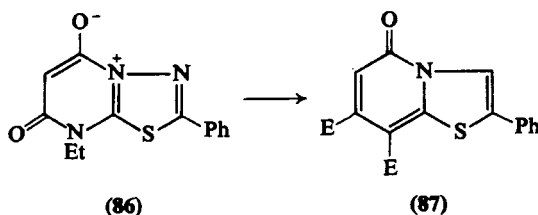
L. THIAZOLOIMIDAZOLINES

On heating with DMAD, the thiazoloimidazoline hydrochloride (**84**) did not give the expected Diels–Alder product **83** but gave the salt **85**;⁶¹¹ a Diels–Alder adduct was obtained from **84** with *N*-phenylmaleimide.



M. MESOIONIC THIAZOLO[3,2-*a*]PYRIMIDINES

Thiazolo[3,2-*a*]pyrimidines-5,7-dione (**86**), refluxed with DMAD for 20 hours in chloroform, gave 65% of the pyridothiazole **87** by elimination of ethyl isocyanate.⁶¹²

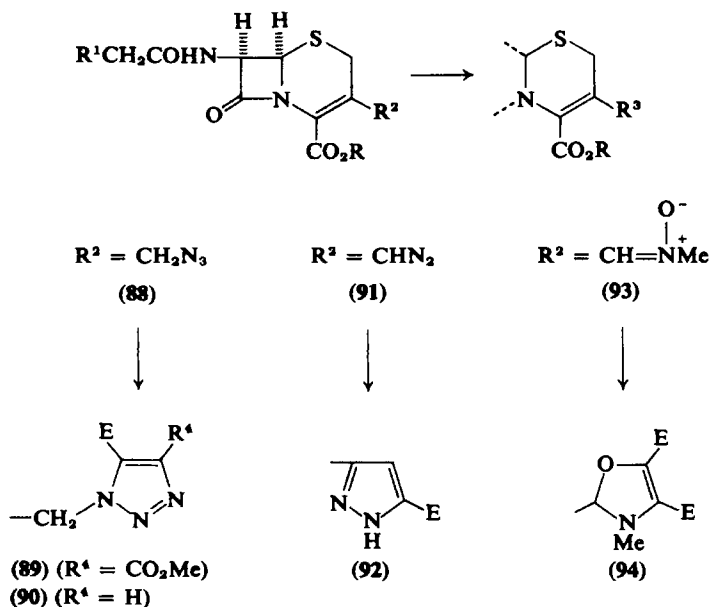


⁶¹¹ Dr. M. T. Cox, personal communication.

⁶¹² R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.* **10**, 487 (1973).

N. CEPHALOSPORINS AND PENICILLINS

The cycloaddition of DMAD and EP to 7-acylamino-3-azidomethyl-3-cephem-4-carboxylic acid derivatives (**88**) gave the expected 1,2,3-triazole derivatives **89** and **90**.⁶¹³ A similar addition of MP to the diazo compound **91** gave **92**,⁶¹⁴ and the nitron **93** gave **94** with DMAD, a rearrangement having taken place.⁶¹⁵



Barton *et al.*⁶¹⁶⁻⁶¹⁸ have shown that the sulfenic intermediates produced thermally from penicillin sulfoxides can be added across acetylenic esters to produce conjugated sulfoxides in good yields. For example, the methyl ester **95** with DMAD afforded the isomeric

⁶¹³ D. Willner, A. M. Jelenevsky, and L. C. Cheney, *J. Med. Chem.* **15**, 948 (1972).

⁶¹⁴ J. L. Fahey, R. A. Firestone, and B. G. Christensen, *J. Med. Chem.* **19**, 562 (1976).

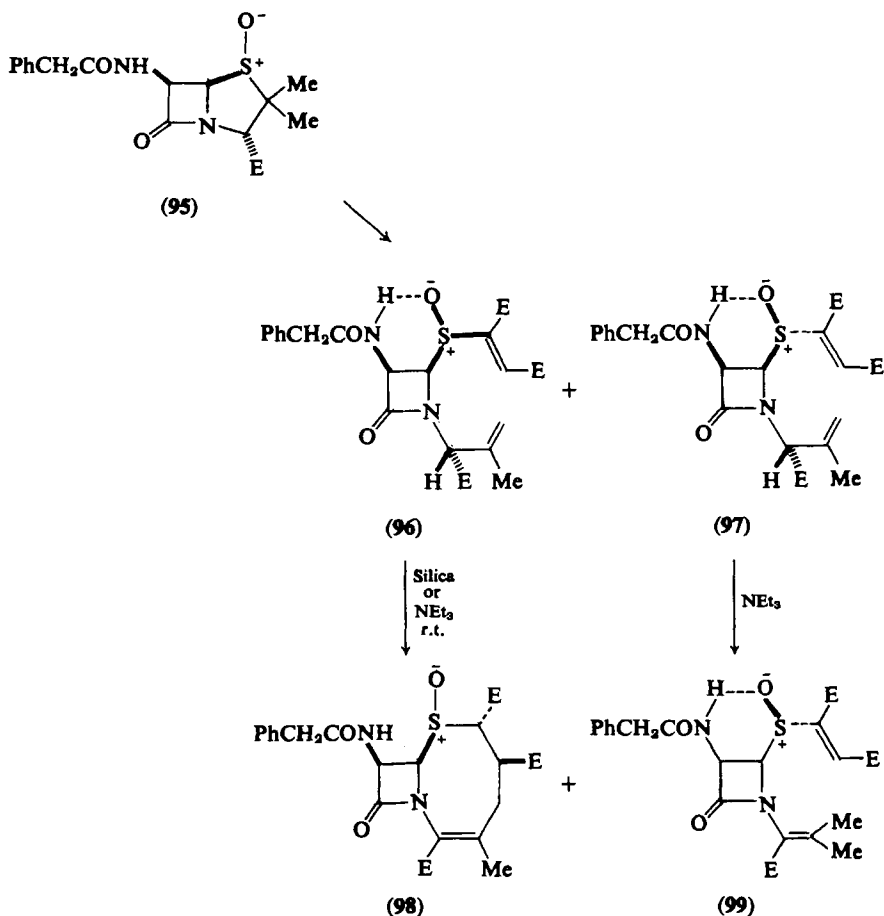
⁶¹⁵ D. O. Spry, *J. Org. Chem.* **40**, 2411 (1975).

⁶¹⁶ D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *Chem. Commun.*, 303 (1973).

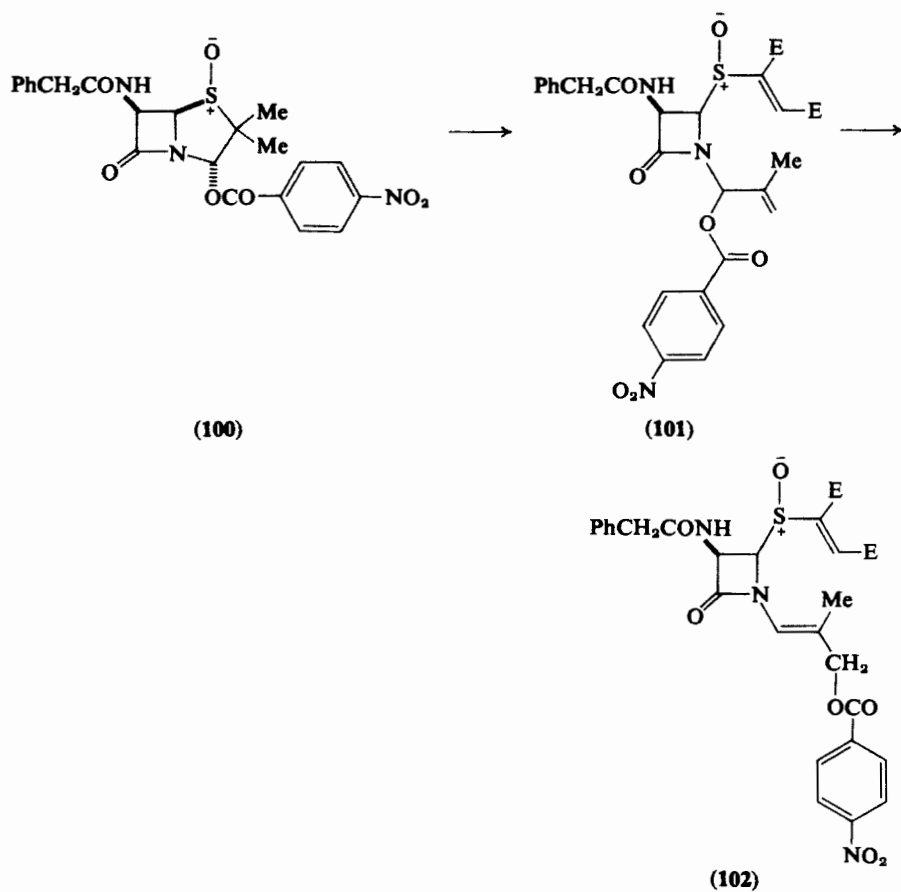
⁶¹⁷ I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. Y. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robinson, and W. G. E. Underwood, *J. Chem. Soc., Perkin Trans. I*, 1187 (1973).

⁶¹⁸ D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J. Chem. Soc., Perkin Trans. I*, 1459 (1974).

sulfoxides **96** and **97** in a 1:1 ratio. The former isomer was unstable and, on silica, slowly cyclized to **98**. Treatment of the mixture of sulfoxides **96** and **97** with triethylamine at room temperature also afforded **98** and the conjugated isomer **99**, and it was shown that the latter was derived from pure **97**.



Reactions were also carried out with EP. In further experiments, DMAD was reacted with the *p*-nitrobenzoate (**100**) to give **102** as the major product derived from the expected isomer **101** by an allylic rearrangement.



ACKNOWLEDGMENT

We are grateful to Dr. G. Procter for his very helpful criticism of the manuscript.

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